7111000G – SENSERYN[1]™

Version: 20 - 20/OCT/2020

1. PRODUCT IDENTIFICATION

Trade Name:	SENSERYN[1]™
Manufacturer:	PROVITAL
Responsible for the Safety Assessment:	Lourdes Mayordomo
Tf./Fax:	3493-7192350/7190294
e-mail:	l.mayordomo@weareprovital.com
Kind of Raw Material:	Active Ingredient
Function of the Ingredient (PCPC Inventory):	Antimicrobial Agents; Antiperspirant Agents; Fragrance Ingredients; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Function of the Ingredient (UE Inventory):	Antimicrobial, Antiperspirant, Fragrance; Hair Conditioning, Skin Conditioning, Skin Protecting

2. PRODUCT COMPOSITION

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

[EU]		CAS	EINECS
Propanediol**	50 - 70 %	504-63-2	207-997-3
		26264-14-2	
Glycerin	30 - 50 %	56-81-5	200-289-5
Humulus Lupulus Extract[1]	1 - 3 %	8016-25-9	---
		8060-28-4	232-504-3
Citric Acid	0,1 - 0,3 %	77-92-9	201-069-1
		5949-29-1	

PCPC [CTFA]		CAS	EINECS
Propanediol**	50 - 70 %	504-63-2	207-997-3
Glycerin	30 - 50 %	56-81-5	200-289-5
Humulus Lupulus (Hops) Extract[1]	1 - 3 %	8016-25-9	---
		8060-28-4	232-504-3
Citric Acid	0,1 - 0,3 %	77-92-9	201-069-1
		5949-29-1	

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:

The CIR Expert Panel concluded that several Humulus lupulus-derived ingredients, including "Humulus lupulus (Hops) Extract", are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing. (CIR Final Report, October 5, 2017)

Hops have been used in the brewing industry for centuries, without any known adverse effect to the health of

consumers. Thus, given the history of long-term and present use in humans with no significant adverse effects, it is considered that hops are safe. (European Medicines Agency, Commitee on Herbal Medicinal Products, EMEA/HMPC/513618/2006, July 2008)

The following substances have the GRAS status ('Generally Recognized As Safe'): Humulus lupulus (21CFR182.20, 21CFR582.20), Glycerin (21CFR182.1320)

The following substances are used as Food Additives permitted for human consume by FDA: Humulus lupulus (21CFR172.560)

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 Cosmetic Ingredient Review (CIR) Expert Panel concluded that the ingredient Propanediol is safe in the cosmetic practices of use and concentrations as described in the safety assessment. (CIR Final Report, June 13, 2018)

The CIR Expert Panel concluded that Citric Acid is safe in the present practices of use and concentration described in this safety assessment. (IJT 2014, 33(S2),16S-46S)

Classification according to Council of Europe (*):

Not classified

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

Cytotoxicity:

Propanediol (RTECS nº TY2010000): IC50 in human-skin cells >2000 µmol/L/48h.

Citric Acid (RTECS no. GE7350000): ICLo Human skin = 60 mg/well/10M, ICLo rabbit-ocular = 5pph/5M, IC50 Dog liver = 1.58 g/L/24H, IC50 Dog kidney = 1.03 g/L/24H, IC50 Human lymphocyte > 200 mg/L/45H, ICLo Human skin = 100 mg/L/24H

Skin Irritation:

SENSERYN (Cod. 71110): Patch Test in 12 volunteers. Product tested at 100%. The results did not show any irritation reaction, so under the conditions tested; this product is considered to have Very Good Skin Compatibility and can be considered NON-IRRITATING.

SENSERYN (Cod. 71110): In vitro skin irritation test (SkinEthic, OECD Test Guidelines Nº 439). Product tested at 100%, topically applied on a reconstructed human epidermis. The results showed a viability higher than 60% therefore under these conditions, the product is classified as NON-IRRITANT at dermal level.

In three different studies the irritability of Humulus lupulus (Hops) Extracts was tested at concentrations from 0.06 to 0.18%. Two of these studies were patch-tests and were conducted on 12 volunteers each during 24 and 48 hours. The third study was a cumulative irritation test with two weeks of duration and 26 subjects. All three studies concluded that Humulus lupulus (Hops) Extract was non-irritant. (CIR Final Report, October 5, 2017)

Propanediol: Propanediol (undiluted) was mildly irritating to rabbit skin in 24-hour occlusive patch tests; Propanediol (undiluted)in volunteers was non-irritating after a single application of test substance. (CIR Final Report, June 13, 2018)

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)

Citric acid (RTECS no. GE7350000): Draize test skin: rabbit 500 mg/24h = mild; rabbit 0.5 ml = moderate.

Skin Sensitization:

SENSERYN (Cod. 71110): HRIPT (Human Repeated Insult Patch Test) in 51 volunteers. Product tested at 10%. The results did not show any irritation or sensitization reaction, so under the conditions tested; this product is considered to have Very Good Skin Compatibility and can be considered NON-IRRITATING and NO-SENSITIZING.

SENSERYN (Cod. 71110): In vitro sensitization study h-CLAT (OECD Protocol Nº 442E). Product tested at different concentrations (1000, 500 and 250 ug/ml) and applied to a culture of human monocytes. The results recorded did not show a significant increase of the markers CD54 and CD86 of the monocytes, therefore this product is considered NON-SENSITIZING.

In four different studies the sensitization of Humulus lupulus (Hops) Extracts was tested at concentrations from 0.125% to 10%. Three of these studies were HRIPT and were conducted on 52, 102 and 102 volunteers during a maximum period of two weeks. The fourth study was a human maximization test and was performed on 26 subjects. All four studies concluded that Humulus lupulus (Hops) Extract was non-sensitizing. (CIR Final Report, 5 October, 2017)

Propanediol: Studies conducted in guinea pigs with an intradermal application at 2.5% and epicutanea at 100% concentration at induction, and an epicutaneous application at 50% and semioclusive at challenge showed that there was non-sensitizing.
In studies with volunteers the results were not sensitizing, with concentrations of 5% to 75% applied at induction and at challenge. (CIR Final Report, June 13, 2018)

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:

SENSERYN (Cod. 71110): Evaluation of the eye irritation potential from the in vitro "Short Time Exposure" Test (STE, according to an adapted version of OECD Protocol Nº 491). Product tested at 0.05% and 5%, applied to a monolayer culture of SIRC cells during 5 minutes. The results showed an average viability higher than 70% in all the experimented conditions tested, therefore the product is considered NO IRRITANT at ocular level.

Propanediol: Eye irritation was evaluated in rabbit eyes with undiluted propanediol obtaining No-to-slight irritation (resolved within 48 hours post-application. (CIR Final Report, June 13, 2018)

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

Citric Acid (RTECS Nº. GE7350000): Standard Draize test, rabbit eye = 750 µg/24h, severe irritation.

Mutagenicity:

SENSERYN (Cod. 71110): Bacterial Reverse Mutation Assay (Ames Test) using 5 strains of Salmonella typhimurium (TA1535, TA1537, TA98, TA100 and TA102), both in the presence and absence of a metabolic activation system (S -9). The product was tested at 5 concentrations between 0.312 y 5 mg/plate. The results did not show a significant increase in the number of revertants in any of the strains, so under the conditions tested, this product is classified as NON-MUTAGENIC.

In two different studies the genotoxicity of Humulus lupulus (Hops) Extract was evaluated at different concentrations (0-10.000µg/plate and 0.5% respectively) in the Ames test using S. typhimurium strains. The test substances were not mutagenic in these assays with or without metabolic activation. (CIR Final Report, October 5, 2017)

Several hop extracts showed weakly mutagenic potential in Salmonella typhimurium strains TA98 and TA. Since these effects was not observed in the other strains it might be a false positive result in the Ames Test. Other assays as the mouse lymphoma test give negative results and confirms that hop extracts are not mutagenics. (European Medicines Agency, Commitee on Herbal Medicinal Products, EMEA/HMPC/513618/2006, July 2008)

Propanediol: A mammalian chromosomal aberration test in vitro in V79 cellular line resulted in negative responses with metabolic activation and positives without metabolic activation only whit 2.5 mg/ml dose. In another in vitro study of chromosomal aberration in mammals reported negative results at concentrations up to 5 mg/ml Propanediol. Also, in an in vivo study in rats (fed 500 ppm of Propanediol for 15 weeks) negative results were recorded, except at some point in the test, probably for a propanediol metabolite. Finally, an in vivo study of micronucleus in mouse was negative (single oral dose of 2150 mg / kg). CIR has evaluated these studies and considers that Propanediol has no mutagenic potential. (CIR Final Report, June 13, 2018)

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:

Humulus lupulus, extract (RTECS nº Mt6606000): TDLo p.o. rat = 200 mg/kg.

Humulus lupulus, water extract (RTECS no.: MT6636000): TDLo oral mouse = 500 mg/kg

Propanediol (RTECS no.TY2010000, Last Updated:200608): LDLo p.o rat = 10g/kg, LDLo i.m. rat = 6 g/kg, LD50 i.p. mice = 4780 mg/kg, LDLo p.o cat = 3 g/kg, LDLo i.v. rabbit = 3 g/kg, LD50 p.o mice = 4500 mg/kg

Propanediol: An approximate lethal dosage of 17 g/kg (70% purity) and > 25 g/kg (99.8% purity) and an LD50 of

14.9 ml/kg were reported in rats by oral route. A LD50 > 20 g/kg was determined in a study in rats by dermal route.Finally, in inhalation studies in rats the animales survived a 4-hour exposure to 2 to 5 g/l. (CIR Final Report, June 13, 2018)

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.

Citric acid (RTECS no. GE7350000): LD50 p.o. rat = 3 g/kg; LD50 i.p. rat = 290 mg/kg; LD50 s.c. rat = 5500 mg/kg; LD50 p.o. mouse = 5040 mg/kg; LD50 i.p. mouse = 903 mg/kg; LD50 s.c. mouse = 2700 mg/kg; LD50 i.v. mouse = 42 mg/kg; LD50 i.v. rabbit = 330 mg/kg; LD16 i.p. rat = 197 mg/kg; LD16 p.o. rat = 5 g/kg; LD16 p.o. mouse = 5440 mg/kg; LDLo i.p. rat = 382 mg/kg; LDLo p.o rat = 83 g/kg; LDLo p.o mouse = 9080 mg/kg; LDLo p.o. rabbit =7 g/kg; TDLo intratraqueal guinea pig = 118 g/kg; TDLo i.v. dog = 64 mg/kg/30M; TDLo i.v. dog = 256 mg/kg/1H; TCLo inhalation guinea pig = 20 pph/10M; TCLo inhalation monkey = 2.5 pph/5M; TCLo inhalation guinea pig = 11528 g/m3/3M; TCLo inhalation rat = 180 mg/m3; TCLo inhalation guinea pig = 19214 g/m3/10M; TCLo inhalation human = 87328 g/m3/0.0083M.

Subchronic and chronic toxicity:

Humulus lupulus, water extract (RTECS no.: MT6636000): TDLo oral mouse = 3000 mg/kg/15D-I

In a study, rats (n=7/group) were fed a high-fat diet supplemented with 1% xanthohumol-rich Humulus lupulus (Hops) Extract for 41 days. There were no mortalities or other adverse effects observed. (CIR Final Report, October 5, 2017)

A study was conducted on the effects of Humulus lupulus (Hops) Extract in concentrations of 2 to 5% on high-fat diets with mice (n=10/group) during 20 weeks. There were no mortalities or other adverse effects observed. (CIR Final Report, October 5, 2017)

Humulus lupulus, extract (RTECS no.: MT6606000): TDLo oral rat = 48 g/kg/8D-C, TDLo oral rat = 3360 mg/kg/8W-C

Propanediol: A rat inhalation study evaluating exposure to Propanediol, up to 1800 mg/l, 6 h/day for 2 weeks (9 exposures total), reported no remarkable results. A NOEL of 1000 mg/kg/day was reported in rats by oral route (CIR Final Report, June 13, 2018)

Propanediol. Repeat-Dose Toxicity test after inhalation administration in rat during 9 exposures, NOEL= 1800 mg/m3. (HSDB-Hazardous Substances Databank no. 8263)

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)

Citric Acid (RTECS no. GE7350000): TDLo p.o. rat = 9.3 g/kg/15d-I; TDLo p.o. rat = 18.6 g/kg/30d-I; TDLo p.o. rat = 12.6 g/kg/21d-I.

Reproductive effects:

Humulus lupulus: Pregnancy category B2: no increase in frequency of malformation or other harmful effects on the foetus from limited use in women. Animal studies are lacking. Lactation category CC: Compatible with breastfeeding but use caution. (The Essential Guide to Herbal Safety, Simon Mills and Kerry Bone, Elsevier, First edition 2005, pp 468)

Humulus lupulus, extract (RTECS nº: MT6606000): TDLo s.c rat =300mg/Kg, female 3 days pre-mating

Propanediol In rat studies by oral route evaluating Propanediol at dose rates up to 1000 mg/kg/day, spermatogenic endpoints were unaffected (90-day exposure duration) and no maternal (dosing on days 6 - 15 of

gestation) or fetal toxic effects were observed (maternal and fetal NOAEL 1000 mg/kg/day). (CIR Final Report, June 13, 2018)

Glycerin (RTECS Nº. MA8050000): rat, i.t. TDL0 = 280 mg/kg, 2 days, male; rat oral TDL0 = 100 mg/kg, 1 day, male; rat, i.t., TDL0 = 862 mg/kg, 1 day, male.

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:

SENSERYN (Cod. 71110): The UV-vis absorption spectrum of the product was evaluated; in accordance to the established in the OECD protocol No. 101. In the absorption range 300-400nm (UVA), the results show that the product does not absorb, therefore the product does not show phototoxic potential.

4. ECOLOGICAL DATA

Biodegradability:

None test of biodegradability have been performed on this product. However, we have been able to conclude that this product can be considered as easily biodegradable due to his composition and the raw material used, considering that the ingredients in this product are from vegetal origin.

Propanediol reached 11 and 16% of its theoretical BOD (Biochemical oxygen demand) using unacclimated and acclimated sewage sludge, respectively, during a 5-day incubation period (Hazardous Substances Databank Number: HSDB-8263)

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

Aquatic Toxicity:

Propanediol: EC50: Daphnia magna age 6-24 hr; Conditions: freshwater. Static, 20 deg C, PH > or= 7.0; Concentration: 8285000 µg/L for 24 hr; EC50: Daphnia magna age 6-24 hr; Conditions: freshwater. Static, 20 degC, PH> or= 7.0; Concentration: 7417000 µg/L for 48 hr; LC50: Carassius auratus weight 3.3 g; Conditions: freshwater, static, 20 deg C, PH 7.0, dissolved oxygen >4.0 mg/L; Concentration >5000000 µg/L for 48 hr (Hazardous Substances Databank Number: HSDB-8263)

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).

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

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.