7527000G – DRENALIP™

Version: 22 - 24/AUG/2015

1. PRODUCT IDENTIFICATION

Trade Name:	DRENALIP™
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-Emollient; Skin-Conditioning Agents-Miscellaneous
Function of the Ingredient (UE Inventory):	Emollient; Skin conditioning
INCI approved in:	Registered in EU, USA, Japan
Japanese Name:	Butcher Broom Extract, ---, ---, ---

2. PRODUCT COMPOSITION

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

[EU]		CAS	EINECS
Propanediol	40 - 60 %	504-63-2 26264-14-2	207-997-3
Aqua	40 - 60 %	7732-18-5	231-791-2
Ruscus Aculeatus Root Extract	2 - 4 %	84012-38-4	281-682-9
Citrus Limon Peel Extract	1 - 2 %	84929-31-7 92346-89-9	284-515-8 296-174-2
Solidago Virgaurea Extract	1 - 2 %	85117-06-2	285-559-0
Astragalus Membranaceus Root Extract	1 - 2 %	94166-93-5	303-391-9
Preservatives			
Sodium Benzoate	0,2 - 0,3 %	532-32-1	208-534-8
Potassium Sorbate	0,2 - 0,3 %	24634-61-5 590-00-1	246-376-1

PCPC [CTFA]		CAS	EINECS
Propanediol	40 - 60 %	504-63-2 26264-14-2	207-997-3
Water	40 - 60 %	7732-18-5	231-791-2
Ruscus Aculeatus Root Extract	2 - 4 %	84012-38-4	281-682-9
Citrus Limon (Lemon) Peel Extract	1 - 2 %	84929-31-7 85085-28-5	284-515-8 285-359-3
Solidago Virgaurea (Goldenrod) Extract	1 - 2 %	85117-06-2	---
Astragalus Membranaceus Root Extract	1 - 2 %	94166-93-5	303-391-9
Preservatives			
Sodium Benzoate	0,2 - 0,3 %	532-32-1	208-534-8
Potassium Sorbate	0,2 - 0,3 %	24634-61-5 590-00-1	246-376-1

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:

The following herbs have been approved by the German Commission E Monographs: Ruscus aculeatus (Published July 12, 1991), Solidago virgaurea (Published October 15, 1987, Revised March 13, 1990)

American Herbal Products Association: Ruscus aculeatus root- Herbs that can be safely consumed when used appropriately (Class 1)

American Herbal Products Association: Astragalus membranaceus root- Herbs that can be safely consumed when used appropriately (Class 1)

American Herbal Products Association: Lemon peel is classified as herb that can be safely consumed when used appropriately (Class 1).

The following substances have the GRAS status ('Generally Recognized As Safe'): Lemon Peel (21CFR182.20).

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.

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.

Classification according to Council of Europe (*):

Ruscus:3, Citrus:3, Solidago:---, Astragalus:---

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

Cytotoxicity:

DRENALIP (Cod. 75270): Neutral Red Release Assay performed using SIRC cell line. Results: CI50>50%, % of mortality at dilution 50% = 22%. Unimportant cytotoxicity.

Skin Irritation:

DRENALIP (Cod.75270): Patch Test on 10 volunteers, occlusive patch for 48 hours, product tested at 15%. No irritant reactions were registered at 15 minutes and 24 hours after patch removal. The clinical cutaneous comaptibility of this product may be judged "Very Good"

Essential lemon oil (RTECS no. OG8300000): Standard draize test mouse skin at 100% = mild irritability, and in rabbit (500 mg/24h) = moderate irritability.

Propanediol. Skin irritation tests in NZW rabbit: undiluted product at 0.5ml was considered to be a Slight irritant. (Supplier data)

Skin Sensitization:

DRENALIP (Cod. 75270). Marzulli and Maibach's Method: Human Repeated Insult Patch Test. Study on 52 volunteers, product tested at 15%. No pathological irritation, nor sensitisation reaction was registered. Drenalip is classified as a No-Sensitizant product.

Astragalus membranaceous is a popular herbal medicine used to treat allergic diseases in East Asia. A study performed in mice confirned tha anti-allergenic activity of this plant: the oral administration of Astragalus root extract, at a dose of 100 mg/kg, inhibit ethe development of dermatitis induced by DNFB. (Biol. Pharm. Bull. 30(8) 1468-1471, 2007)

Propanediol. Skin sensitization tests: Studies performed in guinea pigs by Landsteiner/Draize method and by Magnusson-Kligman method considered the product to be non-sensitizing. Studies in human at product concentration of 50% in 112 volunteers and 75% in 207 volunteers considered the product not to be a primary skin irritant or a sensitizing agent. (Supplier data)

Eye Irritation:

DRENALIP (Cod. 75270): Bovine Cornea Opacity and Permeability Test (BCOP), product tested at 15%. Corneal score at 30 min =0.9, Corneal score at 4h = 2.8. This product is classified as Weakly Irritant.

Propanediol. Eye irritation tests in NZW rabbit: undiluted product at 0.1ml was considered to be Non-irritating and at 0.2 ml was considered to be Practically non-irritating. (Supplier data)

Mutagenicity:

DRENALIP (Cod. 75270): 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 3.4 and 55 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.

Rutin: dose: 2x 2500, 2x1250, 2x625 mg/kg, Micronucleous test in mice: negative in all doses,SCG Test an increase only at the dose 2x1250 mg/kg (Food Chem Toxicol 2002 Jul;40(7):941-7)

Rutin (RTECS nºVM2975000): Mutation in Salmonella typhimurium = 80 ug/plate and = 5 umol/plate/48H; DNA repair in E. coli = 100 mg/L; Specific locus test p.o. Drosophila melanogaster = 50 mmol/L; DNA damage i.p. mouse = 2500 mg/kg/2D-I.

Neohesperidin (RTECS no. DJ2981400): EPA GENETOX PROGRAM 1988 - Negative in BFU Test in Salmonella typhimurium.

Hesperidin: Ames Test on Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 and in E. coli WP2, with and without S-9; dose: 0.033-10 mg/plate; result: no mutagenic (CCRIS-Chemical Carcinogenesis Research Information System, number 3940, last revision date: 20020410).

Hesperidin (RTECS no. MK6650000): TDLo p.o. rat = 12600 mg/kg/6w-C.

Essential lemon oil (RTECS no. OG8300000): TDLo mouse skin = 280 g/kg/33w-I.

Extracts of Astragalus membranaceus root were not mutagenic in a modified Ames test using Salmonella typhimurium TA98 and TA 100. Furthermore, an aqueous extract of this plant was reported to be antimutagenic in that it inhibited benzo-a-pyrene activity in Salmonella typhimurium TA100 (WHO Monographs on selected medicinal plants, Vol 1, pp:56, 1999)

Propanediol. Genetic toxicity tests: This product was considered non-mutagenic in the Ames Test (OECD method no.471), in the HPRT Test (OECD method no. 476), in the chromosome aberrations test (OECD method no.473) and in the in vivo mouse micronucleus test (92/69/EEC Method) (Supplier data)

Acute toxicity:

Ruscus aculeatus, alcohol extract (RTECS nº:VM1975000): LDLo i.v. dog = 830 mg/kg, LDLo i.p. guinea pig = 2 g/kg

Solidago virgaurea, extract (RTECS nº WF2890000):LD50 i.p. mouse = 600 mg/kg; (RTECS nºWF2890700): LD50 i.p. mouse =11200 ug/kg

Ethanolic extract from Ruscus :LD i.p. guinea pigs 1.5 g/Kg (ESCOP 2ª Ed. 2003 pg 442)

Rhizome extracts from Ruscus: LD50 p.o rat 2.07-2.39 ml /Kg ; LD50 p.o mice 24.69-33.73 ml/Kg (ESCOP 2ond Ed. 2003 pg 442).

Ruscogenin and Ruscus saponins : LD50 p.o rats and mice > 3g/Kg.(ESCOP 2ond Ed. 2003 pg 442).

Rutin (RTECS nºVM2975000): LD50 i.p. rat = 2 g/kg; LD50 i.p. mouse =200 mg/kg; LD50 i.v. mouse = 950 mg/kg; LD50 i.p. guinea pig = 2 g/kg; TDLo i.v. mouse = 6 mg/kg; TDLo i.p. mouse = 10 mg/kg.

Astragalus membranaceus, root extract (RTECS no. CJ1682100): TDLo p.o. mouse = 20 mg/kg

No adverse effects were observed in mice after oral administration of root of Astragalus at doses up to 100 g/kg, this dose is several hundred times as high as the effective oral dose in humans. (WHO Monographs on selected medicinal plants, Vol 1, pp:55, 1999)

Astragalus membranaceus, root extract (RTECS no. CJ1682100): TDLo p.o. human= 300 mg/kg

Citrus limon (L.) Burm.f., extract: Acute toxicity study on mouse, intraperitoneal, LD50 > 250 mg/kg (RTECS - Registry of Toxic Effects of Chemical Substances, number: GE8817000, last update: 200012).

Neohesperidin (RTECS no. DJ2981400): TDLo i.p. mouse = 30 mg/kg.

Hesperidin (RTECS no. MK6650000): LD50 i.p. mouse = 1 g/kg; TDLo i.p. mouse = 5 mg/kg; TDLo i.p. mouse = 25 mg/kg.

Essential lemon oil (RTECS no. OG8300000): LD50 p.o. rat = 2840 mg/kg, and rabbit > 5 g/kg.

Naringin (RTECS no. QN6340000): LD50 i.p. rat = 2 g/kg; guinea pig = 2 g/kg; TDLo p.o. rat = 100 mg/kg; i.p. mouse = 30 mg/kg.

Propanediol. Acute toxicity tests: p.o. in rat LD50 = 15800 mg/kg, dermal in rat LD50 > 4200 mg/kg and inhalation in rat, DL > 5000 mg/m3. (Supplier data)

Subchronic and chronic toxicity:

Butcher's broom extract: rabbit 2 g/Kg in diet for 26 weeks.Showed no toxic effects.(ESCOP 2ond Ed. 2003 pg 442).

Ruscogenin o Ruscus saponins : rat p.o 300 mg/Kg for 8 weeks.Showed no toxic effects. (ESCOP 2ond Ed. 2003 pg 442).

Butcher's broom dry extract: taken orally by women 72-75 mg/day for 12 weeks. Showed no toxic effects. (ESCOP 2ond Ed. 2003 pg 442).

Subchronic toxicty study of root of Astragalus membranaceus estract in rats and dogs. These animals were daily administered of product by intra-peritoneum or vein for three months. The product was safe without any distinct toxicity and side effects, the dosage range is 5.7-39.9 g/kg for rataa and 2.85-19.95 g/kg for dogs, which is equal to 70 or 35 times of that of human (0.57 g/kg) respectively. (J Ethnopharmacol. 2007 21;110(2):352-5)

Astragalus membranaceus, root extract (RTECS no. CJ1682100): TDLo p.o. mouse = 2800 mg/kg/10W-I, TDLo p.o. mouse = 3360 mg/kg/12W-I, TDLo p.o. rat = 35000 mg/Kg/7D-C, TDLo i.p. rat = 3630900 mg/kg/91D-I and TDLo i.v. dog = 316680 mg/kg/6W-I

Astragalus membranaceus, root extract (RTECS no. CJ1682100): TDLo p.o. mouse = 210 mg/kg/7D-I, TDLo p.o. rat = 56000 mg/kg/8W-I, TDLo i.v. rat = 42 mL/Kg/3W-I and TDLo i.v. mouse = 560 mg/kg/4w-I

Astragalus membranaceus (var. mongholicus), root, etanol extract, flavonoid content (RTECS no. CJ1682030): TDLo p.o. rat = 840 mg/kg/6W-I and TDLo p.o. rat = 4200 mg/kg/6W-I

Astragalus membranaceus, rhizome, water extract (RTECS no. CJ1682020): TDLo p.o. rat = 2700 mg/kg/6W-I y TDLo p.o. mouse = 280000 mg/kg/28D-I

Hesperidin (RTECS no. MK6650000): TDLo p.o. rat = 2750 mg/kg/22w-I.

Naringin (RTECS no. QN6340000): TDLo p.o. rat = 560 mg/kg/56d-I.

Rutin (RTECS nºVM2975000): TDLo p.o. mouse = 268800 mg/kg/8W; TDLo p.o. mouse = 4200 mg/kg/21D-I; TDLo p.o. rat = 1400 mg/kg/5W-I

Propanediol. Repeat-Dose Toxicity tests: p.o. in rat for 90 days NOEL = 1000 mg/kg/day and inhalation in rat after 9 exposures NOEL= 1800 mg/m3. (Supplier data)

Reproductive effects:

Ethanolic butcher´s broom extract (10%): a daily dose of 2,4 ml started one week before conception and continued until delivery. Showed no toxic effects.(ESCOP 2ond Ed. 2003 pg 442).

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.

Ruscus - Pregnancy category B1: no increase in frequency of malformation or other harmful effects on the foetus from limited use in women. No evidence of increased foetal damage in animal studies (The Essential Guide to Herbal Safety, Simon Mills and Kerry Bone, Elsevier, First edition 2005, pp 306-308).

Propanediol. Prenatal development toxicity test in rat (OECD method no. 414), the product administered at 250 and 1000 mg/kg by oral gavage on gestation days 6-15, was considered non-toxic. Study on effects during reproduction in rats after a 90-day oral administration, there were no effects to reproductive organs and differences in fertility. (Supplier data)

Other data:

The use of Ruscus aculeatus is compatible with breastfeeding (The Essential Guide to Herbal Safety, Simon Mills and Kerry Bone, Elsevier, First edition 2005, pp 306-308).

Ruscus preparations are extremely safe and shows an overall tolerability in clinical studies for the treatment of venous insuffiency(Arznei. 2002;52(4):243-50; J.A.Com.Med.2000 Dec; 6 (6):539-49)

4. ECOLOGICAL DATA

Biodegradability:

Propanediol: BOD5 = 1160000 mg/L (Supplier data)

Aquatic Toxicity:

Propanediol. Acute toxicity tests: Fish (Pimephales promelas) LC50 = 7417 mg/L, Daphnia magna EC50 = 7417 mg/L and growth inhibition of algae EC50 > 10000 mg/L (Supplier data)

Other data:

No data available.

5. CONCLUSION

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.

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