Dermikelp Cream

Ecklonia Maxima Extract 37.5 g/100 g

Clinical Overview

1. Product Development Rationale

The applicant, Lamicare seeks approval of an *Ecklonia maxima* extract formulated in a cream preparations 25 g, 50 g and 100 g tubes for topical administration dated 29 October 2013 (See below dosage unit formula). *Ecklonia Maxima,* sea bamboo, is a species of kelp most typically found along the southern Atlantic coast of Africa up towards Namibia. Phlorotannin derivatives namely phloroglucinol, eckol, 7-phloroeckol, 2-phloroeckol, and a sterol, 24-ethylidine cholesterol have been isolated from *Ecklonia maxima.* **[1]**. Radical scavenging activities for phlorotannins based on experimental studies and theoretical predictions have been reported. Several patents have been filed by different inventors for sea bamboo compositions intended for skin, hair and nail applications. [2].

[1]. M H Maina, Structural investigation of the natural products composition of selected South Africa seaweeds, PhD Thesis, March 2014, University of the Western Cape.
[2]. US20150064213 A1, US20090123406 A1, PCT/IB2014/059294, GB1303469.9,

Dosage Unit formula for Dermikelp cream

Approved name	*Ingredients per 100g*	*Active or inactive*	*Purpose of inactive*
Aqua purificata	46.18 g	Inactive	Vehicle
Ecklonia maxima Extract	37.50g	Active	
Cetearyl Alcohol (and) PEG-20 Stearate	5.50 g	Inactive	Emulsifier
Isopropyl myristate	5.20 g	Inactive	Oil Phase
Cetearyl Alcohol (and)CetearylGlucoside	2.00 g		Emulsifier
Petrolatum	1.50 g	Inactive	Vehicle
Ethylhexylglycerin (and) Phenoxyethanol	1.00 g	Inactive	Preservative
Gluconolactone	0.375 g	Inactive	Preservative
Phenoxyethanol	0.375 g	Inactive	Preservative
Caprylyl glycol	0.175 g	Inactive	Preservative
Citric acid	0.125 g	Inactive	Acidifier
Sodium benzoate	0.125 g	Inactive	Preservative

The formulation indicates that the product contains (five) 5 preservatives. The active: ***Ecklonia maxima*** extract content is 37.5 g/ 100 g product.

2. Indications:

The applicant seeks approval for indications for the use of Dermikelp cream:
DERMIKELP® CREAM is a non-steroidal preparation that reduces skin irritation. It soothes itching associated with skin irritation and is suitable for the symptoms associated with eczema, contact dermatitis, seborrhoeic dermatitis, minor insect bites, allergic skin reactions, soaps, detergents, cosmetics and jewellery.

3. Directions for use:

For external use only.

Apply to the affected area as required. Massage gently into the skin to ensure proper absorption.

DERMIKELP® CREAM can be used daily as required.

4. Studies conducted

The applicant presented studies conducted by Bio Basic, based in Milan, Italy.

Three studies were conducted,

- one on the safety (topical irritant effects);
- two efficacy studies
    - two products were compared for their soothing effects against a non-treatment arm;
    - steroid hormone formulations were compared for their soothing effects:

- ***Study 1: Patch Test DQK-F-003 Record no 1201G06P dated 18/07/2012***

The patch test objective is to evaluate the possible irritant power of a cosmetic product according to the amended Draize classification. The report described the method of the study using a Finn Chamber and with reference to the Declaration of Helsinki and the 76/768 ECC directive for conducting the study. Selection criteria of outpatients with stated. The quantity of products as a dose was indicted allowing skin contact of 24 hours and the execution of the test was described. The evaluation of the cutaneous reaction after the removal of the Finn Chamber was conducted

on the 2nd day at 15 min, 1 hr and 24 h time intervals for erythema and edema of the skin. Number of study subjects 25.

Evaluation (Tables 1 and 2 below)

Table no. 1
Scale of evaluation

Erythema	
No erythema	0
Light erythema (hardly visible)	1
Clearly visible erythema	2
Moderate erythema	3
Serious erythema (dark red with possible formation of light eschars).	4
Edema	
No edema	0
Very light edema (hardly visible)	1
Light edema	2
Moderate edema (about 1mm raised skin)	3
Strong edema (extended swelling even beyond the application area)	4

Table no. 2

Classification of the index of average irritation (classification)

Index	Class
0,5	non irritant
from 0,5 to 2,0	slightly irritant
from 2,0 to 5,0	moderately irritant
from 5,0 to 8,0	highly irritant

Class Amended Draize Classification.

Study Results:

1. **Erythema and edema values:** See table below:

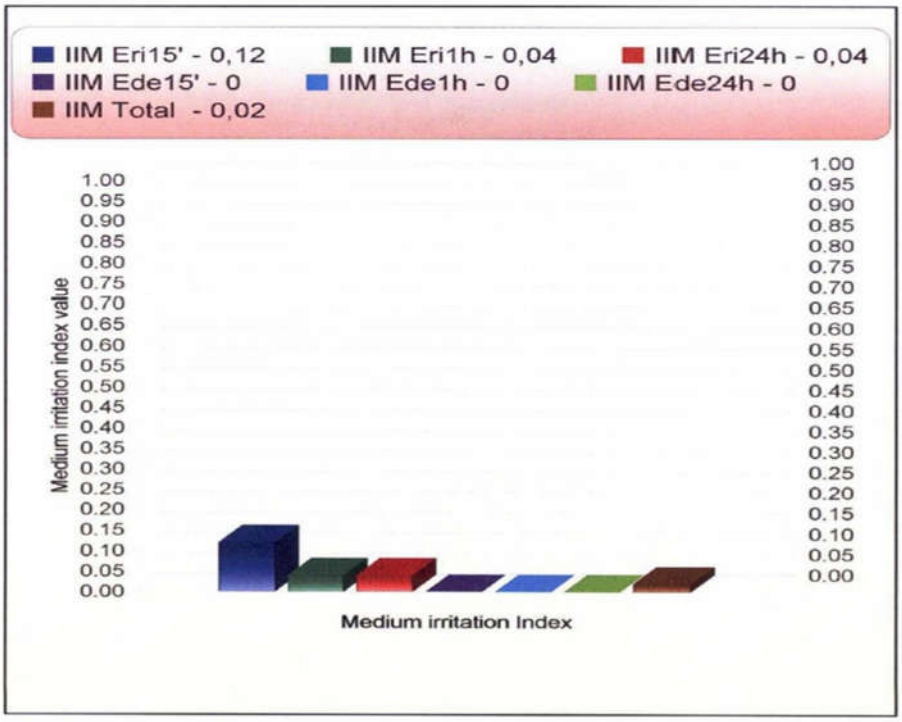
Values of edema and/or erythema

(scale of evaluation: see table no. 1)

Volunteers reference	SEX	Reaction after 15'		Reaction after 1h		Reaction after 24h	
		Erythema	Edema	Erythema	Edema	Erythema	Edema
01ZP	F	0	0	0	0	0	0
02MM	M	0	0	0	0	0	0
03FD	F	0	0	0	0	0	0
04MA	F	0	0	0	0	0	0
05LL	F	0	0	0	0	0	0
06CL	M	0	0	0	0	0	0
07FR	F	0	0	0	0	0	0
08VF	F	1	0	0	0	0	0
09PA	F	0	0	0	0	0	0
10PP	M	0	0	0	0	0	0
11BM	F	0	0	0	0	0	0
12ZA	M	0	0	0	0	0	0
13NB	F	0	0	0	0	0	0
14BB	F	0	0	0	0	0	0
15ER	F	1	0	0	0	0	0
16CLU	M	0	0	0	0	0	0
17DG	M	1	0	1	0	1	0
18MG	M	0	0	0	0	0	0
19PD	F	0	0	0	0	0	0
20VA	F	0	0	0	0	0	0
21SO	M	0	0	0	0	0	0
22BF	F	0	0	0	0	0	0
23SS	F	0	0	0	0	0	0
24TR	M	0	0	0	0	0	0
25NF	F	0	0	0	0	0	0
		0,12	0	0,04	0	0,04	0

2. **Irritant indexes:** See table below

Values and classification of the average irritation indexes
(See table no. 2)



The study investigators concluded that the product DQK-F-003 can be classified as a **non-irritant** product.

3. **Reviewer comment:**

The current values support the claim for the product as a non-irritant for single acute application.

- ***Study 2: "Preliminary evaluation of the soothing power of two cosmetic products through a clinical instrumental test" DKQ-F-003 and DKQ-F-007; Report No. 1201L19F, dated 21 November 2012***

A preliminary study was conducted to evaluate the "soothing" effect of two products namely, DKQ-F-003 and DKQ-F-007 against a non-treatment arm. The study was designed as an open label study with each patient used as its own control with non-treatment regime arm as control (no placebo control arm was included). The study consisted of 10 volunteer males and females in, total between the ages 18-70 years.

The study protocol involved the following: A urea patch was applied for 24 hours to induce redness area of the skin followed my treatments with the two products formulations and non-treatment control

arm. Assessments of the redness and erythema up to 2 hours performed post treatments. Instrumental and Clinical visual assessments were conducted. The instrumental measurements of erythema were conducted using a Mexameter MC18 apparatus. The Clinical visual evaluation assessed the degree of erythema: +, ++, +++. The quantity of product applied during treatment in study was not controlled, with the directions of use of the two products indicated as "use as they are". Investigation time intervals for data collection: totals 2 hour with intervals at T0, T0', T15', T30', T60', T120' min. Photos were taken at investigation time intervals. No investigation was conducted on open skin. The results of the erythema were normalized for each study subject and the average reduction of the erythema was calculated.

Study Results

1. **Erythema (Instrumental and clinical)**

Data of only the DKQ-F-003 (the other product DKQ-F-007, showed weaker response) and the non-treatment arm are presented below.

Evaluation of erythema (Mexameter and clinical evaluation) on treated area with DKQ-F-003

	T0 (basal value)	T0'	IRR	15 min	IRR	30 min	IRR	1 hour	IRR	2 hours	IRR
01EE	100,0	203,0	+++	138,0	++	121,0	+	115,0	+	106,0	
02PL	114,0	225,0	++	167,0	++	135,0	++	112,0	+	109,0	
03EL	106,0	195,0	++	177,0	++	123,0	+	108,0	+	97,0	
04ME	98,0	187,0	++	153,0	++	116,0		99,0		97,0	
05ST	88,0	169,0	++	159,0	++	108,0		91,0		89,0	
06MS	95,0	196,0	+++	153,0	++	127,0	+	104,0	+	99,0	
07LS	89,0	194,0	++	165,0	++	122,0	+	109,0		105,0	
08MC	101,0	197,0	++	165,0	++	116,0		97,0		97,0	
09AG	118,0	245,0	+++	181,0	++	155,0	++	143,0	+	135,0	+
10GD	88,0	202,0	++	176,0	++	120,0	+	95,0		95,0	
MEDIA	99,7	201,3		163,4		124,3		107,3		102,9	

Evaluation of erythema (Mexameter and clinical evaluation) on not treated area

	T0 (basal value)	T0'	IRR	15 min	IRR	30 min	IRR	1 hour	IRR	2 hours	IRR
01EE	98,0	210,0	+++	197,0	+++	192,0	++	185,0	++	166,0	++
02PL	116,0	220,0	++	211,0	+++	218,0	+++	181,0	++	164,0	++
03EL	105,0	193,0	++	185,0	++	196,0	++	187,0	++	167,0	++
04ME	98,0	186,0	++	183,0	++	185,0	++	178,0	++	165,0	++
05ST	86,0	173,0	++	171,0	++	163,0	++	148,0	++	139,0	++
06MS	97,0	206,0	+++	197,0	+++	194,0	++	185,0	++	165,0	++
07LS	90,0	198,0	++	191,0	++	199,0	++	184,0	++	155,0	++
08MC	96,0	200,0	++	195,0	++	179,0	++	185,0	++	172,0	++
09AG	117,0	242,0	+++	249,0	+++	247,0	+++	212,0	+++	167,0	++
10GD	87,0	191,0	++	187,0	++	183,0	++	178,0	++	161,0	++
MEDIA	99,0	201,9		196,6		195,6		182,3		162,1	

% Reduction of the Erythema

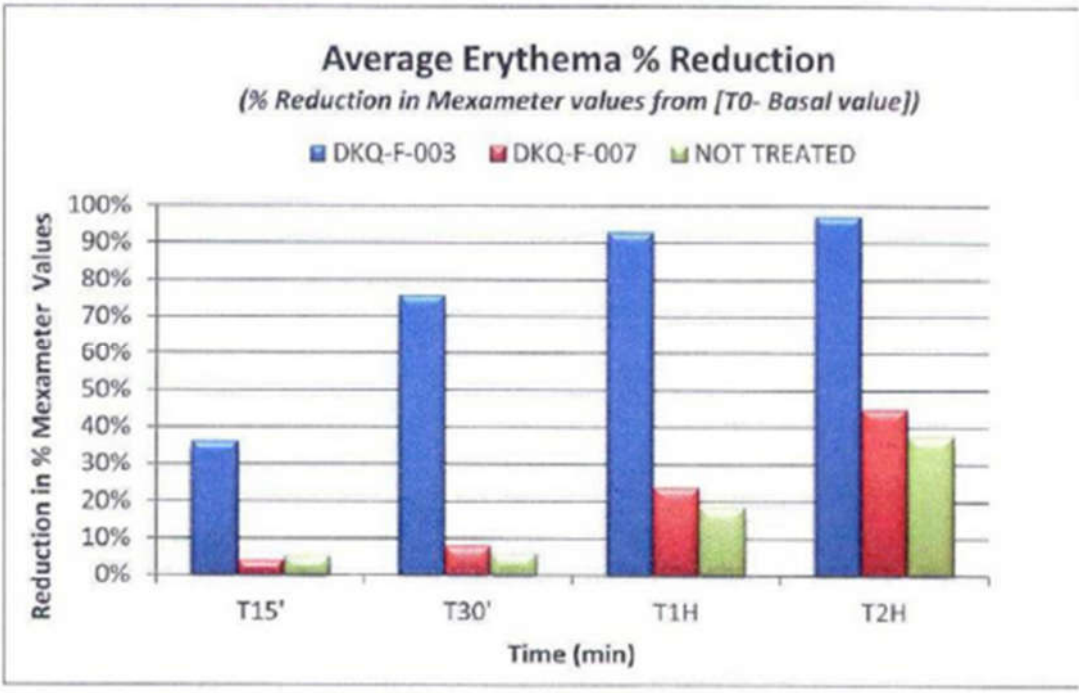
% Reduction of Erithema (instrumental value of Mexameter)

treated area with DKQ-F-003

	T15'	T30'	T1H	T2H
01EE	63,11%	79,61%	85,44%	94,17%
02PL	52,25%	81,08%	101,80%	104,50%
03EL	20,22%	80,90%	97,75%	110,11%
04ME	38,20%	79,78%	98,88%	101,12%
05ST	12,35%	75,31%	96,30%	98,77%
06MS	42,57%	68,32%	91,09%	96,04%
07LS	27,62%	68,57%	80,95%	84,76%
08MC	33,33%	84,38%	104,17%	104,17%
09AG	50,39%	70,87%	80,31%	86,61%
10GD	22,81%	71,93%	93,86%	93,86%
Average	36,3%	76,1%	93,1%	97,4%
Std.Dev	0,2	0,1	0,1	0,1
RSD%	44,18%	7,65%	9,05%	8,20%

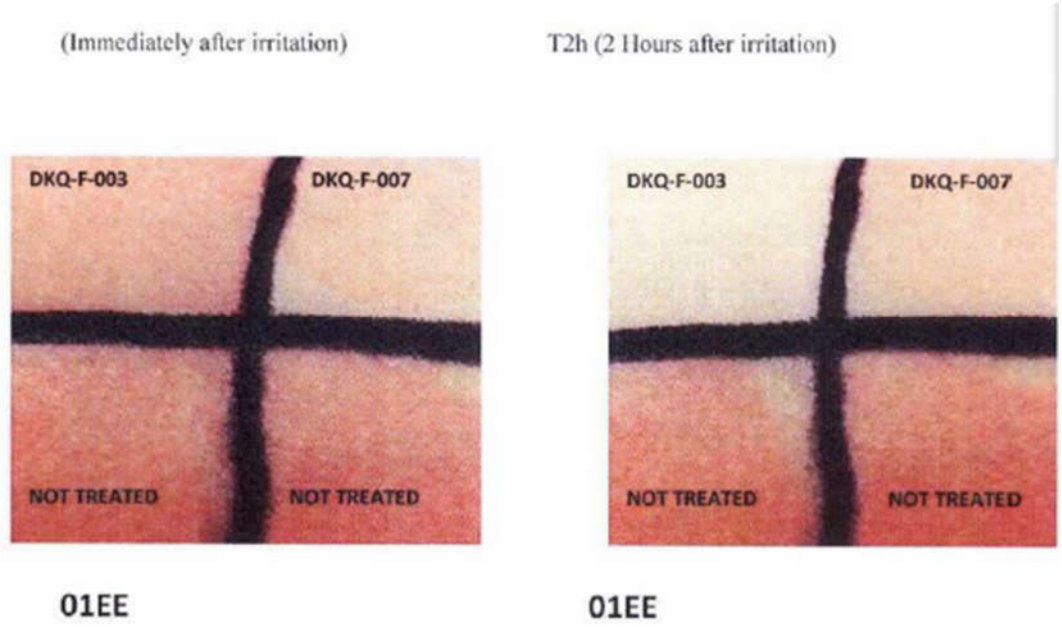
Not treated area

	T15'	T30'	T1H	T2H
01EE	11,61%	16,07%	22,32%	39,29%
02PL	8,65%	1,92%	37,50%	53,85%
03EL	9,09%	-3,41%	6,82%	29,55%
04ME	3,41%	1,14%	9,09%	23,86%
05ST	2,30%	11,49%	28,74%	39,08%
06MS	8,26%	11,01%	19,27%	37,61%
07LS	6,48%	-0,93%	12,96%	39,81%
08MC	4,81%	20,19%	14,42%	26,92%
09AG	-5,60%	-4,00%	24,00%	60,00%
10GD	3,85%	7,69%	12,50%	28,85%
Average	5,3%	6,1%	18,8%	37,9%
Std.Dev	0,0	0,1	0,1	0,1
RSD%	91,24%	137,57%	50,84%	30,72%



2. Clinical visual assessment:

The reduction in the redness of the skin was visually assessed after the urea patch challenge. Typical photos presented below per study subject:



The study investigators concluded that the product DKQ-F-003 exhibits a higher soothing outcome compared to the non-treatment arm. It is also conducted the DKQ-F-007 exhibits no soothing effect.

- ***Study 3: "Comparative soothing effect of steroid hormone containing formulation" DKQ-F-003 and DKQ-F-007; Report No. 1201N03F, dated 9 January 2012***

A comparative study was conducted to evaluate the soothing activity of two steroid hormone containing formulations (Peitel Pomada and Mylocort Cream) against a non-treatment arm.
Identical protocol for the study was followed as described above for Study 2.

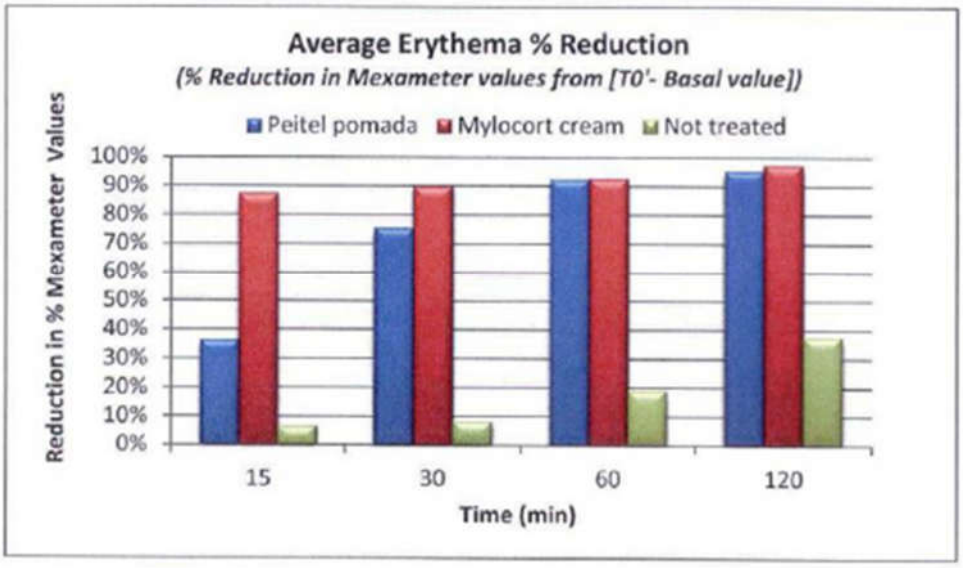
Study Results:

1. **Erythema (Instrumental and clinical)**

Results of the average reduction of the erythema are presented below:

AVERAGE REDUCTION (%) OF ERITHEMA (Mexameter values)

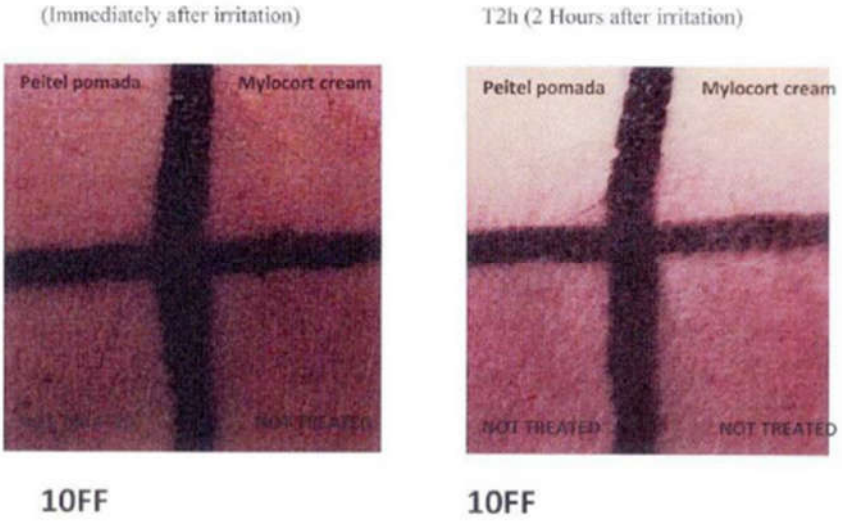
	T15'	T30'	T1H	T2H
Peitel pomada	36,49%	75,54%	92,37%	95,38%
Mylocort cream	87,52%	89,96%	92,70%	97,45%
Not treated	6,68%	8,40%	19,23%	37,64%



The study investigators concluded that the effects of the Mylocort cream are more rapid than the Peitel Pomada. The data non-treatment arm show lower reversal effects, with nearly 40% reversal of the erythema. This effect is similar to that found for Study 2

2. Clinical visual assessment:

The reduction in the redness of the skin was visually assessed after the urea patch challenge. Typical photos presented below per study subject



The study investigators concluded that the two steroidal products exhibit comparable effects at 2 h but that Mylocort cream appears to reduce erythema faster

5. Contraindications:

Hypersensitivity to *Ecklonia maxima*, iodine or any of the other ingredients in **DERMIKELP® CREAM**.

6. Label Claims

DERMIKELP® CREAM is a non-steroidal preparation that reduces skin irritation. It soothes itching associated with skin irritation and is suitable for the symptoms associated with eczema, contact dermatitis, seborrhoeic dermatitis, minor insect bites, allergic skin reactions, soaps, detergents, cosmetics and jewellery.

7. Warnings and Side Effects

Warnings: A Warning for application to "broken skin" has been included.
A stinging or burning sensation may be felt when applied to broken skin.

Side Effects: As per ***Study 1: Patch Test DQK-F-003 Record no 1201G06P dated 18/07/2012*** the product has been classified as non-irritant.

Light erythema may be experienced after application.

8. Literature Information

The applicant included multiple publications of report on the potential of *Ecklonia* spesies. The review focuses on preclinical laboratory investigations. No animal pre-clinical studies on safety and efficacy have been presented. None of the papers had any specific data on *Ecklonia maxima*. All studies included reflect *in vitro* and *in vivo* data on multiple *Ecklonia* species. Several *in vitro* and *in vivo* animal studies have been reported for *Ecklonia cava.* There is a large degree of commonality between constituents present within the different *Ecklonia* spesies, ie. phaephyceae (brown algae). Similar biological activities are expected for these closely related *Ecklonia* species. Skin protect properties have been postulated for marine algea (Tomas and Kim, 2013) Phlorotannin compounds have been implicated in these activities such as inhibition of histamine release. The radical scavenging activity of phlorotannins from *Ecklonia maxima* has recently been reported that could

play an important role in the managing of skin conditions where free radical pathophysiology is underlying (Mwangi et al., 2013).

Recent consensus recommendations on pruritus assessment in clinical trials provides guidance concerning "scoring itching in trials" (Stander et al., 2013).

In vitro studies have shown *Ecklonia Cava* to interact with immune response by method of suppression of the FcεRI receptor that responds to Immunoglobulin E (IgE) on basophils and mast cells. The results of the studies indicated less antigens binding to the receptor with a reduction in histamine release. (*Ecklonia* Cava, examine.com/supplements). *In vitro* investigation into the therapeutic approach for pruritic skin inflammatory diseases have in turn shown potential anti-allergic mechanism by similar means of suppression of binding activity between IgE and FcεRI. It has been concluded that further study of interactions in human cellular systems and the management of various human disease would be of great benefit (Noel Vinay Thomas, Se-Kwan Kim, 2011).

Phlorotanins in *Ecklonia Cava* is reported to be responsible for protection against major oxidative damage. The investigation into the topical application of *Ecklonia cava* as a cosmeceutical, have concluded that the antioxidant, anti-inflammatory, anti-allergy and protective properties is promising for the development of products containing the active component *Ecklonia cava* (WAJP Wijesighe & You-Jin Jeon, 2012). Further observations during *in vitro* studies with methanol extracts form brown algae *Eisenia arborea* have exhibited the potential to treat histamine-related inflammatory diseases and further cytometric analysis has potentiated the anti-allergic mechanism of *Ecklonia cava* as a result of the binding activity between IgE and FcεRI (Noel Vinay Thomas & Se-Kwan Kim, 2013).

The Natural medicines comprehensive database has classified the topical application of *Fucus* species (kelp) as possibly safe (NMDB, monograph Bladderwrack, 2015).

Additionally, *Ecklonia maxima* contains iodine which can possibly be attributed to the mechanism of action of the species. Herbal preparations commonly make use of kelp as a source of iodine.

The European pharmacopeia (*Ph. Eur. 8*) indicate an iodine content of 0,03 – 0,2 % for various kelp species (Martindale, Electronic Ed., 3rd quarter 2016).

Common indications for the topical application of iodine include multiple dermatological conditions, such as dermatitis, erythema nodisum, erythema multiforme, eczema, psoriasis, and antiseptic (NMDB, monograph Iodine, 2015).

Levels of iodine absorption after topical application to the skin ranges between 0,06 % - 0,09 % of the applied dose (Harrison et al, 1963).

A. **Thomas and Kim, Beneficial Effects of Marine Algal Compounds in Cosmeceuticals, Mar. Drugs 2013, 11, 146-164**
B. **Mwangi et al., Isolation, identification and radical scavenging activity of phlorotannin derivatives from brown algae, Ecklonia maxima: An experimental and theoretical study, Free Radicals and Antioxidants 3 (2013) S1 -S10**
C. **Stander et al., Pruritus Assessment in Clinical Trials: Consensus Recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials, Acta Derm Venereol 2013; 93: 509–514**
D. **Ecklonia cava, http://examine.com/supplements/ecklonia-cava/#ref61, p. 1 – 19.**
E. **Noel Vinay Thomas & Se-Kwan Kim, Environmental toxicology and Pharmacology 32 (2011), Review, Potential pharmacological applications of polyphenolic derivatives from marine brown algae, p. 325 – 335.**
F. **W.A.J.P. Wijesinghe & You-Jin Jeon, International Journal of food Sciences and Nutrition, March 2012; 63 (2), Exploiting biological activities of brown seaweed *Ecklonia cava* for potential industrial applications: a review, p. 225 – 235.**
G. **Natural Medicines Comprehensive Database, Monograph, Bladderwrack, dated 13/02/2015.**
H. **Natural Medicines Comprehensive Database, Monograph, Iodine, dated 15/02/2015.**
I. **Martindale, the Complete Drug Reference, Electronic Edition, 3rd Quarter 2016, Seaweeds, Kelps and Wracks.**
J. **Harrison J (1963) The fate of radioiodine applied to human skin. *Health Physics,* 9: 993 – 1000.**

9. Reviewer Comments:

1. The preliminary cosmetic studies were conducted using 10 study subjects between 18 and 70 years of ages. The study protocol further involves a single acute administration of the product and subsequent assessment:
    a. The number of study subjects need to be increased to serve as an efficacy study as compared to the number included for the preliminary cosmetic study.
    b. The number of study subjects does not reflect the application for all ages. However, as a topical preparation with non-irritant properties it is expected to be safe.
    Topical application of **DERMIKELP® CREAM** for over the counter use, is expected to be safe if application is in accordance with the proposed dosing and safety information included in the patient information leaflet.
    c. The current cosmetic studies assessed reduction erythema and redness after induction of redness by the urea patch.
    d. Canada Health Allows the following indications for *Ecklonia cava*:
        i. Humectant
        ii. Skin-Conditioning Agent
    Similar biological activities are expected for closely related *Ecklonia* species with similar constituents.
    e. No results were presented on the effects of administration of this products to "broken skin"
2. The indication for use is based on the formulation which includes only *E. maxima* as an active component. No cortisone or steroidal ingredients has been added to enhance efficacy.
3. Continuous use of the product has not been assessed for safety and potential efficacy.
4. Single acute administration indicated that the product is non-irritant.
5. Literature indicate that the *in vitro* mechanism of action for *Ecklonia* species is attributed to binding activity between IgE and FcεRI which results in possible anti-inflammatory response and reduction in histamine rate.
6. Iodine content within the *Ecklonia* species can also be attributed to potentiate possible activity during topical application. Further investigation would be of great benefit.

10. Conclusion

The applicant seeks approval for the medicinal application for a topical product **DERMIKELP® CREAM**, containing *Ecklonia maxima* extract. The current information submitted on the product investigations are of a preliminary nature with small number of study subjects. The studies have been designed as cosmetic investigations and not as medicinal investigations. Product testing indicate a non-irritant profile when applied topically. Reduction of erythema and redness was observed in the pilot study on humans. A study design to investigate the effect of the product on itching would be useful to explore additional actions of the *Ecklonia maxima*. Pre-clinical studies indicated that the phlorotannins present in the *Ecklonia* spesies exhibit promising biological properties that may present therapeutic potential. Literature evidence suggest therapeutic benefit of *Ecklonia species* based on several *in vitro* studies.

Declaration from the expert

Product details:
Dermikelp Cream

Ecklonia Maxima Extract 37.5 g/100 g

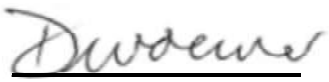
Document: Clinical Overview

Date of compilation: October 2016

Reviewer: Prof. Douglas William Oliver

I, Prof Douglas Oliver, hereby confirm that I have compiled the Clinical Overview of the product Dermikelp Cream, *Ecklonia Maxima* Extract, based on the available Studies and literature included herewith.

Signature:



Prof. Douglas Oliver

06 October 2016
Date