High purity γ-Polyglutamic Acid (γ-PGA) produced through biotechnology

Bio-PGA Na Powder

External and internal Moisturizing for dry skin

FOR SKIN CARE
New moisturizing effect to form film on skin and improve moisture retention capacity in the skin

It spreads smoothly on the skin, and after dryness, the formation of smooth film improves barrier function. Due to improving Pyrrolidine carboxylate and lactic acid, which are the main components of Natural Moisturizing Factor (NMF), improvement of Internal moisturizing will be expected.
**Double moisturizing effect of Bio-PGA Na Powder**

- **Bio-PGA Na**
  - External covering of the skin surface
  - Produce moisturizing factor internally
- **Horny Layer**
- **Epidermis**
  - Water
  - NMF (PCA)

**Improvement of water content in the horny layer**

<table>
<thead>
<tr>
<th>Description</th>
<th>Ratio of electric conductivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1% Bio-PGA Na Powder Solution</td>
<td>250</td>
</tr>
<tr>
<td>3% Glycerin Solution</td>
<td>100</td>
</tr>
</tbody>
</table>

Three healthy people (2 males and 1 female, 20's to 30's), with their written consent, were enrolled as the subjects in this study. Test samples were applied on the dorsal forearm of each subject, and changes of water content in horny layer were measured. Results confirmed that 0.1% Bio-PGA Na Powder solution improved water content in horny layer for 12 hours similar to that of 3% Glycerin Solution.

**Inhibition of Trans Epidermal Water Loss (TEWL)**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0.1% Bio-PGA Na Powder Solution</td>
<td>0.150</td>
</tr>
<tr>
<td>3% Glycerin Solution</td>
<td>0.090</td>
</tr>
</tbody>
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Three healthy people (2 males and 1 female, 20's to 30's), with their written consent, were enrolled as the subjects in this study. Test samples were applied on the dorsal forearm of each subject, and changes of TEWL were measured. According to the results, Bio-PGA Na Powder Solution decreased TEWL when compared to the 3% Glycerin Solution. This confirmed the improvement of barrier function on horny layer of the skin.

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</tr>
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<td><strong>Loss on drying</strong></td>
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</tr>
<tr>
<td><strong>Residue on ignition</strong></td>
<td>37.0 to 50.3%</td>
</tr>
<tr>
<td><strong>Nitrogen</strong></td>
<td>6.7 to 10.6%</td>
</tr>
<tr>
<td><strong>INCI Name</strong></td>
<td>Sodium Polygamma-Glutamate</td>
</tr>
</tbody>
</table>

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PRINTED 2008.09.11 R
RIBOXYL™

NATURAL CELLULAR ENERGIZER

Pure ribose
- Fuels ATP reserves for a fast cell energy recovery
- Global anti-aging action
Riboxyl™ is natural D-ribose, a sugar that occurs in all living cells. Generating new ATP, it restores energy to the skin for a global anti-aging action.

RIBOXYL™, THE SUGAR OF LIFE

Riboxyl™ is pure ribose, a natural pentose obtained by biotechnology from corn seeds. It is a key molecule present in all living cells necessary for the synthesis of ATP (Adenosine Triphosphate) used in every cell metabolic reaction as a source of energy. Over time, cells undergo various stresses (e.g. pollution, physical effort, tobacco smoke and aging) which make the ATP reserves fall, thus altering cell functioning, leading to an acceleration of aging process: appearance of wrinkles, loss of elasticity, dull complexion.

FAST ENERGY REFILL ACTION

Riboxyl™ is a fundamental building block of the ATP molecule. To function efficiently, cells must keep their ATP content at a maximum level.

Each cell has a limited capacity to store ATP. In a healthy organism at normal conditions, the ATP level is maintained constant, due to a permanent turnover (glycolysis, Krebs cycle, ...). However, during stress conditions, the cell energetic need is higher than the recycling capacity and ATP level dramatically falls. When ATP level is too low, the body rebuilds depleted energy supplies with the synthesis of new ATP from ribose, which here is provided by Riboxyl™. By supplementing skin with Riboxyl™, cell energy recovery is accelerated by inducing faster ATP synthesis and providing optimum condition for skin cell to fight signs of aging.

During hypoxia (oxygen depletion), which is an intense stress leading to cell death, cells consume more ATP to survive. The presence of Riboxyl™ limits the decrease in ATP rate by producing de novo ATP rapidly to compensate for the loss.

Generating new ATP, Riboxyl™ restores ATP reserves and replenish cells of energy.
IMPROVEMENT OF CELL FUNCTIONING

By recovering their optimal energy potential, cell metabolic activity is enhanced and attested by a higher oxygen consumption.

Fibroblasts are able to stimulate the synthesis of structuring macromolecules of dermis such as collagen I (+97%), collagen XVII (+70%), fibronectin (+55%), elastin (+37%) and hyaluronic acid (+55%).

This increase in skin component production limits the degradation of tissue, prevents the appearance of wrinkles and enhances elasticity to recover a youthful look.

ANTI-WRINKLE EFFECT AND ELASTICITY IMPROVEMENT

Test protocol
- 21 females (46-65 years old)
- Twice daily application of a cream containing 0.5% Riboxyl™ on face during 28 days
- Elasticity measurements with Dermal Torque Meter at D0 and D28
- Crow’s feet wrinkle measurements by profilometry at D0, D14 and D28

After only 14 days of treatment, Riboxyl™ visibly reduces the appearance of wrinkles and smoothes skin surface. This anti-aging effect is even better after 28 days of treatment.

Skin elasticity is improved to provide more suppleness and optimize skin quality for a better aspect.

Volunteers agree that Riboxyl™ helps the skin to look firmer, smoother, more supple, less dull and revitalized.

BY RELOADING SKIN WITH NEW ENERGY, RIBOXYL™ CLINICALLY IMPROVES THE APPEARANCE OF WRINKLES AND SKIN ASPECT.
FEATURES AND BENEFITS

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>BENEFITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ribose</td>
<td>Stable, odorless and white powder, highly water soluble, easy-to-formulate</td>
</tr>
<tr>
<td>Original mechanism of action</td>
<td>Generation of new ATP to rebuild energetic supplies</td>
</tr>
<tr>
<td>High efficacy</td>
<td>Low dosage</td>
</tr>
</tbody>
</table>
| Boosts synthesis of dermal components | - Visible results after only 14 days:  
  - Wrinkles reduction  
  - Skin elasticity improvement  
  - Complexion enhancement |

PROTECTING DAY CREAM 9.202.01 C84

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>INCI NAMES</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Deionized Water</td>
<td>Water</td>
<td>63.60</td>
</tr>
<tr>
<td>Dermofeel™ PA-3*</td>
<td>Sodium Phytate (and) Water (and) Alcohol</td>
<td>0.10</td>
</tr>
<tr>
<td>FDC Red 4 Solution 0.1%</td>
<td>Water (and) CI 14700</td>
<td>0.30</td>
</tr>
<tr>
<td>Dermosoft™ LP*</td>
<td>Caprylyl Glycol (and) Glyceryl Caprylate (and) Glycerin (and) Phenylpropanol (and) Water</td>
<td>1.00</td>
</tr>
<tr>
<td>B Glycerin</td>
<td>Glycerin</td>
<td>5.00</td>
</tr>
<tr>
<td>Satiaxane CX 911</td>
<td>Xanthan Gum</td>
<td>0.30</td>
</tr>
<tr>
<td>Amigel</td>
<td>Sclerotium Gum</td>
<td>0.30</td>
</tr>
<tr>
<td>C Amisol™ Soft</td>
<td>Behenyl Alcohol (and) Glyceryl Stearate (and) Lecinthin (and) Glycine Soja (Soybean) Sterols</td>
<td>4.00</td>
</tr>
<tr>
<td>D Dub Inin</td>
<td>Isononyl Isononanoate</td>
<td>7.00</td>
</tr>
<tr>
<td>Crodamol W</td>
<td>Stearyl Heptanoate (and) Stearyl Caprylate</td>
<td>5.00</td>
</tr>
<tr>
<td>Dermofeel™ GSC*</td>
<td>Glyceryl Stearate Citrate</td>
<td>1.00</td>
</tr>
<tr>
<td>DC 200.5 Cs</td>
<td>Dimethicone</td>
<td>4.00</td>
</tr>
<tr>
<td>Vitapherole E-1000</td>
<td>Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil</td>
<td>0.20</td>
</tr>
<tr>
<td>E Riboxyl™</td>
<td>Ribose</td>
<td>1.00</td>
</tr>
<tr>
<td>Exo-P™</td>
<td>Water (and) Butylene Glycol (and) Alteromonas Ferment</td>
<td>1.00</td>
</tr>
<tr>
<td>Deionized Water</td>
<td>Water</td>
<td>2.00</td>
</tr>
<tr>
<td>F Suprem™ Nature Thé Vert</td>
<td>Water (and) Helianthus Annuus (Sunflower) Seed Oil (and) Lecithin (and) Polyglyceryl-3 Diisostearate (and) Glycerin (and) Glyceryl Stearate (and) Camelia Sinensis Leaf Extract</td>
<td>2.00</td>
</tr>
<tr>
<td>G SJ Touch 1</td>
<td>Polymethyl Methacrylate</td>
<td>2.00</td>
</tr>
<tr>
<td>H Eclat 4008</td>
<td>Fragrance</td>
<td>0.20</td>
</tr>
</tbody>
</table>

pH: 5.0 - 5.5  - Viscosity (Rhea ELV 8, spindle 4, 6 rpm, 3 mn): 20 000 - 30 000 mPa.s

* Distributed in France by Lucas Meyer Cosmetics and Unipex Solutions France.

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**SEPICALM™ VG**

The first Lightener & Soother

Association of Palmitoylproline with a water lily flower extract for a NEW CONCEPT OF LIGHTENERS

**SO WHITE**

IN VIVO TESTING PROCEDURE:
- SEPICALM VG at 3%
- 30 asian volunteers
- Application area: Normal skin & age spots
- Evaluation before & after 3 and 3 months of treatment:

Significant lightening effect on normal Asian skin and age spots after only 2 months of treatment (formula 7057)

**POLYVALENT EFFICACY WITH NEW MODE OF ACTION**

1. Decreases pigmentation induced by inflammatory stress (UV, irritation, pollution, acne...)
2. Decreases keratinocytes inflammation mediators induced by stress (Interleukin 1, Endothelin Tand Cyclooxygenase)

In vitro tested on keratinocytes and pigmentation reconstructed epidermis submitted to UV

**SEPICALM VG**

Decreases 'basal pigmentation' linked with normal conditions or genetic ageing

Upstream genetic reduction of tyrosinase expression via a new biological pathway

**SO CALMING**

SEPICALM VG: THE FIRST LIGHTENER WITH A SOOTHING EFFECT (already used in the cosmetic field for its soothing effect due to a modulation of inflammation mediators induced by skin stress)

When combined with AHAs, reduces stinging intensity felt by sensitive skins

SEPICALM VG: A possible antagonist of the Wnt signalization pathway leading to a decrease in tyrosinase genetic expression

**SO EASY TO USE**

SEPICALM VG CAN BE EASILY INCORPORATED UP TO 3% in all types of whitening, lightening, and soothing projects

Clear yellow liquid - Lipophilic

More at www.seppic.com
Nota

The analytical specifications warranted are only those mentioned on the certificate of analysis supplied with each delivery of the product.

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www.seppic.com

Subsidiary of the AIR LIQUIDE group

C/3535/GB/01/March 2007
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Double moisturizing effect of Bio-PGA Na Powder

Improvement of water content in the horny layer

Inhibition of Trans Epidermal Water Loss (TEWL)

Three healthy people (2 males and 1 female, 20's to 30's), with their written consent, were enrolled as the subjects in this study. Test samples were applied on the dorsal forearm of each subject, and changes of water content in horny layer were measured. Results confirmed that 0.1% Bio-PGA Na Powder solution improved water content in horny layer for 12 hours similar to that of 3% Glycerin Solution.

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PRINTED 2008.09.11 R
Red Pepper or Capsicum annum has been used for a variety of medicinal applications ranging from digestive to analgesic. Cultivated for more than 7,000 years the fruit of this plant has widespread importance both nutritionally and economically.

Capsicum is generally recognized for its content of capsaicin, the active responsible for the hot burning sensation when chilies are ingested. While Capsaicin has been used as a topical analgesic to treat pain and inflammation associated with arthritis there is often associated redness. Capsaicin’s role in relation to the reduction of pain is complex. On one hand Capsaicin has the ability to bind to the Valinoid Receptor (VR-1), which acts as a polymodal integrator for noxious stimuli. An ability which is shared by various lipoxygenase products as well as some more common phytochemicals such as eugenol, zingerone, vanillin and cannabionoids. VR-1 a member of the transient receptor potential (TRP) super family acts by modulating cellular calcium levels.

Capsaicin has been shown to induce apoptosis in many types of cancer cells. It is now thought that this is due to the localized increase in reactive oxygen species. This is only part of the story with regard to activity of Capsicum because it is clear that there are other components present in the fruit of the plant that can mobilize immune function. Perhaps more importantly Capsaicin inhibits angiogenesis. It is somewhat interesting that a product known to produce redness inhibits angiogenesis. The erythema found with topical application is no doubt a result of the increased ROS levels and not directly a result of increased circulation.

But as with most plants, the activity of a single purified phytochemical does not always explain the activity of a less refined extract. Capsicum has widely been show to contain a high level of antioxidants ranging from ascorbic acid and glutathione to more robust enzymes such as Superoxide Dismutase.

It has also been shown that by fermenting Capsicum a product is formed that will increase glutathione levels while at the same time stimulating immune function. This provided an interesting starting point for a new product. What if we were able to provide some of the benefits of a Capsicum extract without any of the associated irritation?
In an effort to achieve that goal we fermented the macerated fruit of *Capsicum annum* with *Saccharomyces cerevisiae*. This approach was intended to combine the anti-irritant benefits of a yeast extract with the known properties of Capsicum. What we found however was a product that increased circulation without producing associated visual erythema. As the epidermis contains no blood vessels it is nourished by diffusion from the dermis. In order to have healthy radiant skin it is critical to have optimal circulation.

Microvascular perfusion was measured using the PeriScan System, which is a Laser Doppler Perfusion Imaging system intended for non-invasive imaging of superficial tissue blood perfusion. The reported results are relative to biological control. A 5-subject panel consisting of 5 Caucasian females between the ages of 32 and 43 was assembled and provided with two products: one containing 1% of AC DermaPeptide MicroC and another containing 3% of AC DermaPeptide MicroC. To ensure accuracy for all tests, panelists abstained from using lotions, creams or any other cosmetic moisturizers on the test site for a period of three days prior to the tests' initiation. The test area was located on the inner forearm region between the wrist and elbow. A gentian violet surgical skin marker and standard template delineated two 2 cm by 2 cm (4cm²) test sites. 1% and 3% AC DermaPeptide MicroC products were applied at a concentration of 2.0 mg/cm² for three consecutive days. The results clearly indicate that AC DermaPeptide MicroC significantly increases dermal circulation for improved epidermal dispersion.

The same 5 subject panel was used to determine whether or not the use of AC DermaPeptide MicroC induces epithelial erythema using a Minolta CR-200 Chromameter interfaced with a DP-100 Color Computer System. This system detects subtle changes in color that are imperceptible to the human eye. Although no human erythema is detected with the human eye with the use of either 1% or 3%...
AC DermaPeptide MicroC, a slight color change is detectable when using the Minolta CR-200.

During the fermentation process a biotransformation takes place, which creates a capsaicinoid that has increased solubility, additional cell metabolism increasing factors and anti-irritant properties. Unlike most capsicum extracts, AC DermaPeptide MicroC contains a functional active capsaicinoid that is water soluble. Cell metabolism factors are important for maintaining skin clarity and create a "healthy glow". While collagen synthesis is important for the improvement of skin’s resiliency, elasticity and texture. Additionally an increase in collagen synthesis is equated with an improvement in the appearance of firm and supple skin.

AC DermaPeptide MicroC is useful in a variety of cosmetic and cosmeceutical products, which range from anti-aging creams and skin clarifiers to soothing warming lotions and gels.

References:
4 Jeong-Ki Min, Kyu-Yeon Han, Eok-Cheon Kim, Young-Myeong Kim, Sae-Won Lee, Ok-Hee Kim, Kyu-Won Kim, Yong Song Gho, and Young-Guen Kwon (2004) Capsaicin Inhibits in Vitro and in Vivo Angiogenesis CANCER RESEARCH 64, 644–651, January 15
HYDRACTIN® optimises the water balance of the epidermis. The natural energy building block ATP stimulates the cell metabolism of the skin. It is essential for maintaining the osmotic equilibrium in the epidermis and this actively regulates its water balance. Algin, a water-retentive gel derived from sea algae, forms a hydrofilm on the skin and reduces the transepidermal water loss. The enzyme papain from the tropical fruit papaya removes old skin cells and promotes skin regeneration.

HYDRACTIN® thus ensures a fresher appearance and boosts moisture and natural energy.
SCIENTIFICALLY PROVEN EFFECTS

- Immediate improvement in skin moisture of up to + 38% after 1 hour (in-vivo study)
- Long-term improvement in skin moisture of up to + 14% after 28 days (in-vivo study)

ACTIVE INGREDIENTS

ATP

The vitalising cell factor ATP stimulates the metabolism of the skin. ATP is essential for maintaining the osmotic equilibrium of the epidermis and thus actively intervenes in the regulation of the water balance of the epidermis.

Algin

Algin, a natural water store derived from sea algae, forms a film of moisture on the surface of the skin. Through its water-retaining and film-forming properties it protects the skin against evaporation.

Papaya Extract

Papaya extract with the enzyme papain gives the skin a more youthful appearance. Through its protein splitting effect, the enzyme papain helps to remove dead flakes of skin. Metabolic processes and the growth of new skin cells are activated.

SIGNIFICANCE OF WATER IN THE EPIDERMIS

1. Flexibility and elasticity
   Hydration of keratin fibres in corneocytes

2. Formation of the NMW
   Enzymatic splitting of filaggrin / profilaggrin

3. Formation of lamellar lipid matrix
   - Double lipid layers consisting of
     (a) free fatty acids
     (b) ceramides
     (c) cholesterol

4. Regeneration
   Desquamation of corneocytes through enzymatic splitting of corneodesmosomes
SKIN MOISTURE (in-vivo short-term study)

Test formulations with HYDRACTIN® versus placebo

Method: Hydration of the stratum corneum
Implementation: Single treatment with 3% or 6% HYDRACTIN®, 16 test subjects, placebo: 0% HYDRACTIN®, age 48; measuring device: Corneometer®
Result: Effective skin moisturisation, increase of up to 38% compared with placebo; lasting effect: still 20% more skin moisture after 5 hours.

Application and Processing Information
Moisturising skin care for face and body. Suitable for emulsions (W/O and O/W) and gels.

Recommended Use Level: 2 – 8%

INCI: EU: Glycerin, Aqua, Disodium Adenosine Triphosphate, Carica Papaya Fruit Extract, Phenoxyethanol, Algin, Sodium Hydroxide USA: Glycerin, Water, Disodium Adenosine Triphosphate, Carica Papaya (Papaya) Fruit Extract, Phenoxyethanol, Algin, Sodium Hydroxide Japan: Glycerin, Onsen-Sui, Disodium Adenosine Triphosphate, Carica Papaya (Papaya) Fruit Extract, Phenoxyethanol, Algin, Sodium Hydroxide

SKIN MOISTURE (in-vivo long-term study)

Test formulations with HYDRACTIN® versus placebo

Method: Hydration of the stratum corneum
Implementation: 28 days 1 x daily treatment with 3% or 6% HYDRACTIN®, 16 test subjects, placebo: 0% HYDRACTIN®, age 48; measuring device: Corneometer®
Result: Long-term effect as moisturiser confirmed. Increase in skin moisture of up to 14% after 28 days.
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Version: 02/2014
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Each cell has a limited capacity to store ATP. In a healthy organism at normal conditions, the ATP level is maintained constant, due to a permanent turnover (glycolysis, Krebs cycle, ...). However, during stress conditions, the cell energetic need is higher than the recycling capacity and ATP level dramatically falls. When ATP level is too low, the body rebuilds depleted energy supplies with the synthesis of new ATP from ribose, which here is provided by Riboxyl™. By supplementing skin with Riboxyl™, cell energy recovery is accelerated by inducing faster ATP synthesis and providing optimum condition for skin cell to fight signs of aging.

During hypoxia (oxygen depletion), which is an intense stress leading to cell death, cells consume more ATP to survive. The presence of Riboxyl™ limits the decrease in ATP rate by producing de novo ATP rapidly to compensate for the loss.

**Generating new ATP, Riboxyl™ restores ATP reserves and replenish cells of energy.**
IMPROVEMENT OF CELL FUNCTIONING

By recovering their optimal energy potential, cell metabolic activity is enhanced and attested by a higher oxygen consumption.

Fibroblasts are able to stimulate the synthesis of structuring macromolecules of dermis such as collagen I (+97%), collagen XVII (+70%), fibronectin (+55%), elastin (+37%) and hyaluronic acid (+55%).

This increase in skin component production limits the degradation of tissue, prevents the appearance of wrinkles and enhances elasticity to recover a youthful look.

ANTI-WRINKLE EFFECT AND ELASTICITY IMPROVEMENT

Test protocol
- 21 females (46-65 years old)
- Twice daily application of a cream containing 0.5% Riboxyl™ on face during 28 days
- Elasticity measurements with Dermal Torque Meter at D0 and D28
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Skin elasticity is improved to provide more suppleness and optimize skin quality for a better aspect.

Volunteers agree that Riboxyl™ helps the skin to look firmer, smoother, more supple, less dull and revitalized.

BY RELOADING SKIN WITH NEW ENERGY, RIBOXYL™ CLINICALLY IMPROVES THE APPEARANCE OF WRINKLES AND SKIN ASPECT.
FEATURES AND BENEFITS

<table>
<thead>
<tr>
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<tr>
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<td>Low dosage</td>
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<tr>
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<tr>
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PROTECTING DAY CREAM 9.202.01 C84

INGREDIENTS

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pH: 5.0 - 5.5  – Viscosity (Rheo ELV 8, spindle 4, 6 rpm, 3 mn): 20 000 - 30 000 mPa.s

* Distributed in France by Lucas Meyer Cosmetics and Unipex Solutions France.

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High purity γ-Polyglutamic Acid < γ-PGA > produced through biotechnology

Bio-PGA Na Powder

External and internal Moisturizing for dry skin

FOR SKIN CARE

New moisturizing effect to form film on skin and improve moisture retention capacity in the skin.

It spreads smoothly on the skin, and after dryness, the formation of smooth film improves barrier function. Due to improving Pyrrolidone carboxylate and lactic acid, which are the main components of Natural Moisturizing Factor (NMF), improvement of internal moisturizing will be expected.

ICHIMARU PHARCOS Co., Ltd.
www.ichimaru.co.jp
Double moisturizing effect of Bio-PGA Na Powder

Improvement of water content in the horny layer

Inhibition of Trans Epidermal Water Loss (TEWL)

Three healthy people (2 males and 1 female, 20's to 30's), with their written consent, were enrolled as the subjects in this study. Test samples were applied on the dorsal forearm of each subject, and changes of water content in horny layer were measured. Results confirmed that 0.1% Bio-PGA Na Powder solution improved water content in horny layer for 12 hours similar to that of 3% Glycerin Solution.

Three healthy people (2 males and 1 female, 20's to 30's), with their written consent, were enrolled as the subjects in this study. Test samples were applied on the dorsal forearm of each subject, and changes of TEWL were measured. According to the results, Bio-PGA Na Powder Solution decreased TEWL when compared to the 3% Glycerin Solution. This confirmed the improvement of barrier function on horny layer of the skin.

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ICHIMARU PHARCOS Co., Ltd.
www.ichimaru.co.jp

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In addition, the contents represented or described in these materials may concern with intellectual property rights owned by others, so that you are respectfully requested to understand and consider that the use and handling of these materials are to be dealt with finally on your own responsibility.
MARRUBIUM STEMS GX™
Marrubium vulgare stems

IRB STEMS
THE WIDEST RANGE OF
PURE AND SELECTED
PLANT STEM CELLS
RICH IN PHENYLPROPANOIDS
SPECIFIC FOR EACH CELL LINE

by sederma
MARRUBIUM VULGARE STEMS

Marrubium vulgare, also known as White Horehound or Marrubio, is an edible herbaceous plant of the Lamiaceae family, spontaneously growing in temperate areas of Europe, America and Asia. Horehound medicinal properties were esteemed by the Romans and the Arabs. It is often used in the popular medicine as a remedy for respiratory conditions and to improve the digestive function. The plant has also anti-inflammatory properties and is used externally for skin problems.

HTN™ biotechnology, exclusively owned by IRB, is the unique total eco-sustainable process able to physiologically orientate the production of specific substances involved in defensive responses of the plant against environmental physical and biological stress such as phenylpropanoids. Through the in vitro culture of plant stem cells in protected and highly controlled conditions IRB achieves the production of these substances with considerable biological properties.

THE DETOXIFICATION SYSTEM

The skin is the largest organ of the human body and one of its major functions is to defend the body from many different environmental stresses such as UV, chemical irritants, heavy metals and other pollutants, known as xenobiotics. This continuous exposure will result in skin irritation followed by decreased barrier function and penetration of the substances in the body.

To manage this challenge, our skin has developed a complex detoxification system made of molecules and enzymes that can neutralize the external substances. This important protective function is performed by two enzymatic systems known as the Phase I and Phase II enzymes.

Phase I enzymes are involved in oxidation, reduction and hydrolysis of the foreign substances and are, in some cases, responsible for their bio-activation, hence increasing their potential harmfulness.

Phase II enzymes modify the xenobiotics to achieve complete detoxification by conjugating the toxic molecules with hydrophilic residues and making them easier to excrete. Among the Phase II enzymes there are also many antioxidant enzymes like SOD, catalase, heme oxigenase and thioreduxin reductase.

The genetic activation of Phase II enzymes is under control of the nuclear transcription factor Nrf2 which is normally located in the cell cytoplasm and bound to the repressor Keap1. Following increase of the oxidative stress or xenobiotic levels, the Nrf2 separates from Keap1 and enters into the cell nucleus where it activates the transcription of the detoxification, antioxidant and cytoprotective proteins (Phase II enzymes).

Nrf2 levels in the nucleus can be increased by plant molecules (eg. sulforaphane) so that the detoxification system can be alerted and pre-activated. These substances are known as second-generation antioxidants to be distinguished form the traditional first-generation antioxidants with mainly radical scavenging properties (eg. vitamin C).
THE WHEN:

THE FIRST AND UNIQUE THIRD GENERATION ANTIOXIDANT: ENSURING MULTI-PHASE PROTECTION THROUGH RADICAL SCAVENGING AND MAXIMISATION OF SKIN SELF DEFENSIVE SYSTEMS

THE WHY:

HTN™ TECHNOLOGY

Thanks to the HTN™ technology Marrubium vulgare stems are rich of phenylpropanoids, active substances involved in defensive responses of the plant, and particularly FORSYTHOSIDE B and VERBASCOSIDE.*

<table>
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<tr>
<th>Properties</th>
<th>1st generation antioxidant</th>
<th>2nd generation antioxidant</th>
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<tbody>
<tr>
<td>FORSYTHOSIDE B</td>
<td>antioxidant</td>
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</tr>
<tr>
<td>activator of Nrf2</td>
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<td>✓</td>
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<tr>
<td>inducer of Phase II enzymes</td>
<td></td>
<td>✓</td>
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<tr>
<td>VERBASCOSIDE</td>
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</tr>
<tr>
<td>inducer of Phase II enzymes</td>
<td></td>
<td>✓</td>
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</table>

Marrubium vulgare stems constitute therefore the first and unique third generation antioxidant able to ensure to the skin a multi-phase protection against a wide range of oxidative and environmental stresses:

› immediate protection through strong radical scavenging
› long-term protection through maximisation of skin self defensive systems

0 3 12 24 96

Immediate antioxidant activity

Marrubium vulgare stems Third generation antioxidant

1st generation antioxidant

2nd generation antioxidant

Long-term antioxidant protection

ANTIOXIDANT ACTIVITY
The TEAC (Trolox Equivalent Antioxidant Capacity) method is commonly used to evaluate the antioxidant capacity of a substance compared with that of Trolox, a water soluble derivative of vitamin E.

Marrubium vulgare stems are rich of substances with a strong antioxidant activity, more than 2 times as efficient compared to common natural antioxidant benchmarks such as resveratrol and vitamin C.

ACTIVATION OF Nrf2
Human keratinocytes (HaCat) have been incubated for 24 hours with forsythoside B and verbascoside at increasing concentrations (0.006-0.015%) and the nuclear level of transcription factor Nrf2 has been assessed by Western blotting.

Forsythoside B and verbascoside dose dependently increase the levels of Nrf2 protein thus activating the physiological detoxification system of the human keratinocytes and hence the synthesis of Phase II enzymes.
Heme oxygenase 1 (HO-1) is a Phase II enzyme normally present also in human skin where it plays an antioxidant defensive role. In fact several stimuli such as oxidative stress, cytokines and bacterial compounds can considerably induce its synthesis thus improving the skin self defensive systems.

Human keratinocytes (HaCat) have been incubated, at different times, with forsythoside B (0.015%) and verbascoside (0.012%) and the expression levels (mRNA) of heme oxygenase have been assessed by quantitative PCR analysis.

The mRNA level of the protective enzyme heme oxygenase was strongly increased by forsythoside B and verbascoside in a time dependent manner.

Especially forsythoside B increased the expression level up to 8000%, if compared with untreated control.

This stimulating activity also resulted to be dose dependent for both substances (data not shown).

Consequent to the gene expression induction, western blot analysis confirmed that the protein level of heme oxygenase in HaCat was also increased.

Forsythoside B and verbascoside significantly induce the expression and the synthesis of the Phase II enzyme heme oxygenase 1 in human keratinocytes thus improving their physiological self defensive system.
**STIMULATING EFFECT ON PHASE II ENZYMES IN 3D HUMAN EPIDERMIS**

Transcriptional effects of Marrubium vulgare stems were evaluated on reconstructed human epidermis in order to assess effects on Phase II enzymes.

After 24 hours of incubation with the ingredient* (0.125%) the mRNA expression level of typical Phase II enzymes was evaluated by quantitative PCR.

(*) This test has been performed on the powder form of *Marrubium vulgare* cell cultures in order to avoid experimental interferences.

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Marrubium vulgare stems increase the expression levels of the enzymes thioredoxin reductase 2 (TXNRD2) and glutathione S-transferase I (GSTP1). These Phase II enzymes are directly involved in the response to xenobiotics mediated by Nrf2 activation.

**Marrubium vulgare stems are able to potentiate the enzymes belonging to the endogenous cytoprotective system by activation of the Nrf2 transcription pathway.**

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**TXNRD2** is a dimeric NADPH-dependent enzyme that catalyzes the reduction of thioredoxin and is a key enzyme in the regulation of the intracellular redox environment.

**GSTP1** is a member of glutathione S-transferases, a family of enzymes that play an important role in detoxification by catalyzing the conjugation of many xenobiotics with reduced glutathione to facilitate their excretion.
THE HOW:

COSMETIC USES
> detoxifying formulations
> anti-stress day/night creams
> anti-pollution creams
> photo-ageing prevention

POTENTIAL CLAIMS
> Marrubium vulgare stems constitute the first and unique third
generation antioxidant
> ensure multi-phase protection: immediate antioxidant activity and
long-term protection
> maximise skin self defensive systems
> enhances the capacity of the skin to resist to oxidative stress (also
UV induced)
> protect the skin against environmental stresses

RECOMMENDED CONCENTRATION:
> 1 - 3%

FORMULATION GUIDELINES:
> compatible with O/W emulsions, serum, ...
> pH ≤ 6
> introducing during the cooling phase (<50°C)

PRODUCT SPECIFICATIONS

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<th>Product code</th>
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<tr>
<td>Product name</td>
<td>MARRUBIUM STEMS GX™</td>
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</table>
| Product composition | Marrubium vulgare cell cultures 20%
glycerin 80%
xanthan gum 0.3% |
| INCI Name | Glycerin, Marrubium Vulgare Meristem Cell Culture, Xanthan Gum |

BIBLIOGRAPHY
- A. Matkowski, M. Piółrowska, Antioxidant and free radical scavenging activities of some medicinal plants from the Lamiaceae, Fitoterapia 2006, 77(55), 346-53
This information and further technical advice are based on our present knowledge and experience and we reserve the right to make any changes according to further developments and acquisition of new data. The only guaranteed analytical specifications are those appearing in the certificate of analysis sent with each delivery. Performance of the product described herein should be verified by testing carried out only by qualified experts. Experimental results are only referred to test conditions specified and we will not be responsible for any results obtained with different set of conditions or dosage below recommended range. Claim ideas are offered solely for consideration, investigation and verification of the recipient of this document. IRB will not assume any expressed or implied liability in connection with any use of this information.
RIBOXYL™

NATURAL CELLULAR ENERGIZER

Pure ribose
- Fuels ATP reserves for a fast cell energy recovery
- Global anti-aging action
**RIBOXYL™ IS NATURAL D-RIBOSE, A SUGAR THAT OCCURS IN ALL LIVING CELLS. GENERATING NEW ATP, IT RESTORES ENERGY TO THE SKIN FOR A GLOBAL ANTI-AGING ACTION.**

---

**RIBOXYL™, THE SUGAR OF LIFE**

Riboxyl™ is pure ribose, a natural pentose obtained by biotechnology from corn seeds. It is a key molecule present in all living cells necessary for the synthesis of ATP (Adenosine Triphosphate) used in every cell metabolic reaction as a source of energy. Over time, cells undergo various stresses (e.g. pollution, physical effort, tobacco smoke and aging) which make the ATP reserves fall, thus altering cell functioning, leading to an acceleration of aging process: appearance of wrinkles, loss of elasticity, dull complexion.

---

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By reloading skin with new energy, Riboxyl™ clinically improves the appearance of wrinkles and skin aspect.
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</table>

pH: 5.0 - 5.5  - Viscosity (Rheo ELV 8, spindle 4, 6 rpm, 3 mn): 20 000 - 30 000 mPa.s

* Distributed in France by Lucas Meyer Cosmetics and Unipex Solutions France.

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SYN®-COLL is based on a small peptide developed to reduce any type of wrinkles. Clinical trials have shown that SYN®-COLL is capable of reducing and changing the type and aspect of wrinkles that add years to your appearance. Try it and you will see the difference within a short time.

PRODUCT DESCRIPTION
The first signs of aging in the skin typically begin with superficial wrinkles. Therefore it is easily understandable that anti-wrinkle products play an important part as anti-aging products. Over the last few years peptides became an important part among the wrinkle-reducing products. SYN®-COLL is an aqueous, unpreserved, glycerine-based solution of a small peptide. It stimulates the collagen synthesis in human fibroblasts.

BACKGROUND
Skin aging and, in particular, chronic UV exposure lead to degenerative changes in skin characterized by distinct alterations in the composition of the dermal extracellular matrix (ECM). The consequences are manifold such as increased skin fragility, leathery skin appearance and formation of wrinkles. Collagen represents the main component of the ECM of the dermal connective tissue. Thrombospondin I (TSP) is a multifunctional protein that activates the latent but biologically inactive form of TGF-β (Tissue Growth Factor). TGF-β is known as the key element in the synthesis of collagen. TSP binds with the sequence Arg-Phe-Lys to the inactive TGF-β complex, inducing a release of active TGF-β. A molecule able to activate TGF-β would therefore be the ideal product as an effective wrinkle-repairing molecule to accelerate new collagen production. SYN®-COLL is a patented innovative approach that is based on Pentapharm’s many years of experience in synthesizing peptides for the pharmaceutical industry. SYN®-COLL has a unique sequence to mimic the human body’s own mechanism to produce collagen via TGF-β. SYN®-COLL actively compensates for any collagen deficit in the skin and makes the skin look younger.
EFFICACY

ANTI WRINKLE EFFECT OF SYN®-COLL

The study was performed on 60 volunteers. SYN®-COLL has been compared against placebo and against a reference substance. Both products have been used at the recommended use level calculated for their active principle. The study lasted 84 days with a twice-daily application.

SIGNIFICANT DECREASE IN CUTANEOUS RELIEF

Using the PRIMOS® technique, parallel stripe patterns are projected on the sample with successive phase shift. The analysis of fringe deformations provided a qualitative as well as quantitative evaluation of each height profile.

MACROPHOTOGRAPHS

Macrophotographs are done with a Nikon® D1 digital camera. The photographs are taken in standardized, indirect light.

After 84 days of twice-daily application of 2.5% SYN®-COLL parameters average relief (Rz) and maximum relief (Rt) significantly decreased by -12%: -22 µm and -36 µm respectively (p= 0.05) characterizing smoothing and anti-wrinkle effects.

COMPARISON OF PRODUCT EFFICACY

Both products have been used at the recommended use level. SYN®-COLL at 2.5% (25 ppm peptide) and the reference substance Palmitoyl Pentapeptide-3 at 10 ppm (equivalent to a use level of 10% of the market available product calculated for the active peptide). SYN®-COLL clearly showed a higher efficacy for all tested parameters.
Ra: average roughness
Rt: maximum difference between the highest peak and the deepest furrows
Rz: mean value of these different maxima

A decrease of the Ra expresses a smoothed relief.
A decrease of the Rt and Rz expresses a decrease of the wrinkles’ depth.

ADDITIONAL INFORMATION
Moreover, according to the answers of the objective evaluation questionnaire, the majority of the volunteers have appreciated the products for their organoleptics characteristics (aspect, texture, facility of spreading and penetration). A majority have noticed freshness and moisturizing sensation after application. More than 60 % of all volunteers reported a general modification of the skin and an improvement of the crow’s feet at the same time. 93 % of the volunteers will continue the use of a SYN®-COLL containing formula.

CONCLUSION
Clinical trials have shown that the active principle of SYN®-COLL is capable of reducing and changing the type and aspect of wrinkles that add years to your appearance. Try SYN®-COLL and you will see the difference within a short time.

TECHNICAL INFORMATION
PRODUCT SPECIFICATIONS
Appearance : colorless to slightly yellowish, clear liquid
Peptide content : 900-1300 ppm
Relative density (20°C) : 1.15-1.22
Refractive index (25°C) : 1.410-1.440
Microbial count : < 100 CFU/ml
Specified pathogens : absent

PRESERVATION AND MICROBIOLOGY
SYN®-COLL contains no preservative. SYN®-COLL is free of specified pathogens. The amount of non-pathogenic microorganisms with less than 100 CFU per ml of SYN®-COLL meets the CTFA microbiology guidelines.

SAFETY AND ECOLOGY
Standard and well-defined safety testing has been performed on SYN®-COLL which has proved the product to be safe for cosmetic use. The data available do not indicate any environmental risks. The manufacturing process is designed to meet the criteria for the assessment of safety, health and protection of people and of the environment set out in the Responsible Care Program.
PROCESSING AND DOSAGE

SYN®-COLL could be processed either warm (for maximum 2 hours at 80°C) or cold. SYN®-COLL is stable in the pH-range of 3.0 to 7.0. In formulations, SYN®-COLL is compatible with ethanol at concentrations of up to 50%. For skin care preparations, we recommend the addition of 1 to 3% SYN®-COLL. Basic Guide Formulations are available upon request.

STORAGE AND SHELF LIFE

SYN®-COLL should be stored in the original sealed container protected from light in a clean place at a temperature between 2 and 8°C. If stored under the recommended conditions, SYN®-COLL remains stable for at least 3 years. In order to avoid secondary microbial contamination, following opening, the content of the containers should be used immediately since SYN®-COLL does not contain any preservative.

GENERAL PRODUCT INFORMATION

Trade Name : SYN®-COLL
Product Code : 800421
INCI Name (CTFA) : Glycerin, Palmitoyl Tripeptide-5
EU-Labelling Name : Not listed
Chemical Name : Palmitoyl-lysyl-valyl-lysine bistrifluoracetate salt
CAS No : 623172-56-5
Customs Tariff No : 3824.9098 999
Shelf life : 3 years

COMPOSITION

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<th>A) Ingredient(s)</th>
<th>INCI Name #</th>
<th>Amount *</th>
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<td>As listed in the CTFA Dictionary</td>
<td>Palmitoyl Tripeptide-5</td>
<td>F</td>
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<td>B) Additives</td>
<td>INCI Name #</td>
<td>Amount *</td>
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<td>Solvents</td>
<td>Water</td>
<td>C</td>
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<td></td>
<td>Glycerin</td>
<td>A</td>
</tr>
<tr>
<td>Preservative</td>
<td>None</td>
<td>---</td>
</tr>
<tr>
<td>Others (buffers, antioxidants, colorants)</td>
<td>None</td>
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# CTFA Dictionary
* FDA-Code (A = > 50%, B = 25-50%, C = 10-25%, D = 5-10%, E = 1-5%, F = 0.1-1%, G = < 0.1%)

REMARK

Although these data and information have been prepared with the utmost possible care, we reserve the right to make changes due to product improvement and other considerations.

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Pentapharm Ltd, Engelgasse 109, P.O. Box, CH-4002 Basel / Switzerland
Phone : +41-61-706 48 48, Fax : +41-61-319 96 19, www.pentapharm.com
HYDRACTIN® optimises the water balance of the epidermis. The natural energy building block ATP stimulates the cell metabolism of the skin. It is essential for maintaining the osmotic equilibrium in the epidermis and this actively regulates its water balance. Algin, a water-retentive gel derived from sea algae, forms a hydrofilm on the skin and reduces the transepidermal water loss. The enzyme papain from the tropical fruit papaya removes old skin cells and promotes skin regeneration.

HYDRACTIN® thus ensures a fresher appearance and boosts moisture and natural energy.
SCIENTIFICALLY PROVEN EFFECTS

- Immediate improvement in skin moisture of up to + 38% after 1 hour *(in-vivo study)*
- Long-term improvement in skin moisture of up to + 14% after 28 days *(in-vivo study)*

ACTIVE INGREDIENTS

**ATP**

The vitalising cell factor ATP stimulates the metabolism of the skin. ATP is essential for maintaining the osmotic equilibrium of the epidermis and thus actively intervenes in the regulation of the water balance of the epidermis.

**Algin**

Algin, a natural water store derived from sea algae, forms a film of moisture on the surface of the skin. Through its water-retaining and film-forming properties it protects the skin against evaporation.

**Papaya Extract**

Papaya extract with the enzyme papain gives the skin a more youthful appearance. Through its protein splitting effect, the enzyme papain helps to remove dead flakes of skin. Metabolic processes and the growth of new skin cells are activated.

SIGNIFICANCE OF WATER IN THE EPIDERMIS

- **1. Flexibility and elasticity**
  - Hydration of keratin fibres in corneocytes

- **2. Formation of the NMW**
  - Enzymatic splitting of filaggrin / profilaggrin

- **3. Formation of lamellar lipid matrix**
  - Double lipid layers consisting of:
    - a) free fatty acids
    - b) ceramides
    - c) cholesterol

- **4. Regeneration**
  - Desquamation of corneocytes through enzymatic splitting of corneodesmosomes
SKIN MOISTURE (in-vivo short-term study)

Test formulations with HYDRACTIN® versus placebo

**Method:** Hydration of the stratum corneum

**Implementation:** Single treatment with 3 % or 6 % HYDRACTIN®, 16 test subjects, placebo: 0 % HYDRACTIN®, age 48; measuring device: Corneometer®

**Result:** Effective skin moisturisation, increase of up to 38 % compared with placebo; lasting effect: still 20 % more skin moisture after 5 hours.

![Graph showing skin moisture against placebo (%).](image)

**Skin Moisture against Placebo (%)**

<table>
<thead>
<tr>
<th>Hours</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>3 % HYDRACTIN®</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
<td>12%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>6 % HYDRACTIN®</td>
<td>+10%</td>
<td>+12%</td>
<td>+14%</td>
<td>+16%</td>
<td>+18%</td>
<td>+20%</td>
</tr>
</tbody>
</table>

SKIN MOISTURE (in-vivo long-term study)

Test formulations with HYDRACTIN® versus placebo

**Method:** Hydration of the stratum corneum

**Implementation:** 28 days 1 x daily treatment with 3 % or 6 % HYDRACTIN®, 16 test subjects, placebo: 0 % HYDRACTIN®, age 48; measuring device: Corneometer®

**Result:** Long-term effect as moisturiser confirmed. Increase in skin moisture of up to 14 % after 28 days.

![Graph showing skin moisture against placebo (%).](image)

**Skin moisture against placebo (%)**

<table>
<thead>
<tr>
<th>Hours</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>3 % HYDRACTIN®</td>
<td>+10%</td>
<td>+12%</td>
<td>+14%</td>
<td>+16%</td>
<td>+18%</td>
<td>+20%</td>
</tr>
<tr>
<td>6 % HYDRACTIN®</td>
<td>+14%</td>
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</tbody>
</table>

Application and Processing Information

Moisturising skin care for face and body. Suitable for emulsions (W/O and O/W) and gels.

**Recommended Use Level:** 2 – 8 %

**INCI:**
- **EU:** Glycerin, Aqua, Disodium Adenosine Triphosphate, Carica Papaya Fruit Extract, Phenoxethanol, Algin, Sodium Hydroxide
- **USA:** Glycerin, Water, Disodium Adenosine Triphosphate, Carica Papaya (Papaya) Fruit Extract, Phenoxethanol, Algin, Sodium Hydroxide
- **Japan:** Glycerin, Onsen-Sui, Disodium Adenosine Triphosphate, Carica Papaya (Papaya) Fruit Extract, Phenoxethanol, Algin, Sodium Hydroxide
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