

HyaCare® Filler CL

The topical wrinkle smoother

- Instantly fills fine lines & wrinkles.
- Topical alternative to injectables.
- Thoroughly hydrates the skin and improves skin resilience.
- Contains unique, cross-linked hyaluronic acid particles & is preservative free.
- Has super water-absorbing properties.
- Has improved stability to enzymatic degradation.
- Appears to smoothen skin surface.
- Recommended usage level: 0.5 – 5%

INCI Name (PCPC name)

Aqua; Ethylhexyl Stearate; Sodium Hyaluronate Crosspolymer; Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate; Sodium Isostearate

| Chemical and physical properties (not part of specifications) | |
|---|---|
| Form | white to off-white W/O emulsion |
| Active matter | approx. 4% cross-linked Hyaluronic Acid spheres |

Cross-linked Hyaluronic Acid (HA) is well known for its use as a dermal filler. Dermatologists inject it directly into the skin to physically fill up wrinkles from within. Many consumers dislike this invasive and expensive approach. Therefore, they are searching for and would benefit from cosmetic alternatives which mimic the immediate wrinkle reducing properties of dermal fillers.

HyaCare® Filler CL is a W/O emulsion containing small particles of cross-linked Hyaluronic Acid. The average particle size is approx. 700 nm. Due to the cross-linking of Hyaluronic Acid, HyaCare® Filler CL has superior water-binding properties comparable to that of a super-absorbing polymer.

Properties

- Super water-absorbing properties of HyaCare® Filler CL

The super water-absorbing properties of HyaCare® Filler CL can be demonstrated by adding 1.5 volumes water to 1 volume of the emulsion. The water is completely absorbed resulting in a solution with increased viscosity, and an increase in the particle size (Fig. 1).

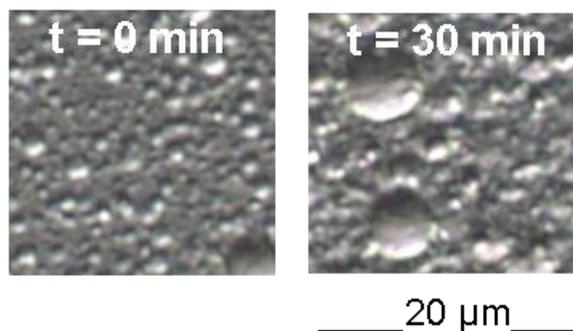


Fig. 1: Particle size of HyaCare® Filler CL before (t = 0 min) and after the addition of water (t = 30 min)

In contrast, the same W/O emulsion containing non-cross-linked Hyaluronic Acid is not able to take up water (data not shown).

In vitro stability of HyaCare® Filler CL against enzymatic degradation

To investigate the stability of HyaCare® Filler CL, the polymer was incubated with mammalian hyaluronidase (a HA degrading enzyme),

Method: Cross-linked Hyaluronic Acid (CL-HA) was isolated from HyaCare® Filler CL by ethanolic precipitation, repeatedly washed with ethanol, and freeze-dried. 5 mg/ml of the isolated cross-linked Hyaluronic Acid were incubated in a phosphate buffer with 0.41 mg/ml of a mammalian hyaluronidase from bovine testes (Type I-S, 400 - 1 000 U/mg, Sigma-Aldrich). Linear Hyaluronic Acid, at the same concentration, was used as control. Enzymatic degradation was quantified photometrically by determination of liberated reducing sugars.

Results: Whereas linear HA was prone to degradation by the hyaluronidase, no significant degradation of cross-linked Hyaluronic Acid (CL-HA) occurred (Fig. 2). Cross-linking thus offers the benefit of superior stability against enzymatic degradation. This may enable HyaCare® Filler CL to provide longer lasting moisturization.

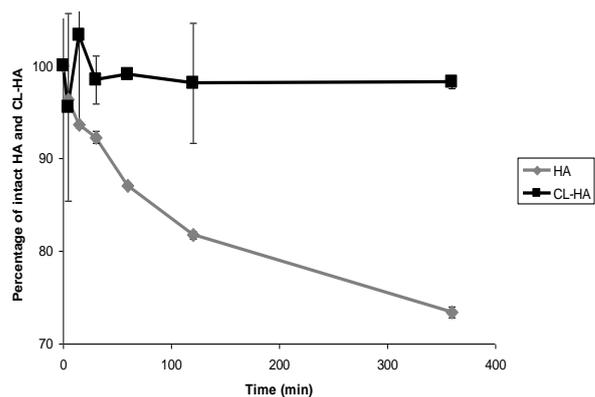


Fig. 2: Stability of CL-HA against enzymatic degradation compared to non-cross linked Hyaluronic Acid (HA)

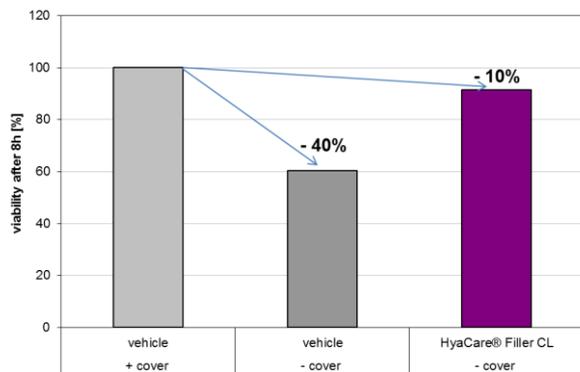
- HyaCare® Filler CL protects a 3D skin model from drying

To investigate the hydration effect of HyaCare® Filler CL, artificially dried skin models were analyzed with and without application of HyaCare® Filler CL.

Method: 3D skin models (SkinEthic) were topically treated either with a formulation containing 0.1 % HyaCare® Filler CL or a vehicle formulation for 1 h at 37 °C, 5% CO₂. In order to mimic dry skin conditions, the skin models were then incubated in a sterile laminar flow cabinet without plate cover for 8 h.

Following that incubation time, cell viability was analyzed by MTT-assay, and the appearance of the skin models was evaluated by histological analysis using Hematoxylin and Eosin staining.

Results: Drying of vehicle-treated skin models under laminar flow led to a 40% decrease in cell viability compared to the control that was protected with a plate cover. When HyaCare® Filler CL was applied to skin models prior to the drying-step, this effect was dramatically reduced. The cell viability in this case after 8 h of drying was only slightly reduced by 10% compared to the control skin models. Monitoring of cell viability over 8 hrs revealed that HyaCare® Filler CL even provides a



superior long term effect compared to the vehicle.

Fig. 3: Cell viability (MTT-assay) after drying the skin models (n=3 each) for 8 h with or without treatment.

The histologic images (Fig. 4) show that drying the skin models has an effect on the structure of the whole epidermis. Following 8h exposure to air with vehicle only applied on the surface, the skin equivalent *stratum corneum* (SC) appears less uniform and well-ordered. There is also a detachment of the SC from the underlying viable epidermal layer due to drying out of the skin models (Fig. 4a). When HyaCare® Filler CL is applied prior to the drying step, these effects are not observed (Fig. 4b). The SC and the underlying layers of the epidermis look very tight and better structured, much more similar to the appearance of a skin model incubated with a cover (data not shown). These observations are in agreement with the higher cell viability compared to the vehicle treatment that was observed in the MTT assay (Fig. 3). Therefore, HyaCare® Filler CL acts as a protective cover for the skin model samples, and minimizes drying upon air exposure.

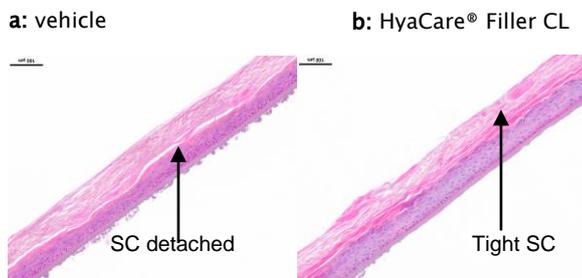


Fig. 4: Histology images of Hematoxylin and Eosin stained SkinEthic skin models after 8 h under different cultivation conditions. Hematoxylin stains cell nuclei in blue and Eosin stains proteins in red.

The superior water binding capacity of HyaCare® Filler CL may therefore provide superior moisturization properties and impart long-term protection for reconstructed epidermal models.

- **In vivo evaluation of HyaCare® Filler CL on skin**

The topical dermal filler properties of HyaCare® Filler CL were examined. **Method:** A formulation containing the cross-linked Hyaluronic Acid spheres was applied to skin and the affected area was imaged using PRIMOS Pico, a contactless method of measuring wrinkles.

Results: It was observed that HyaCare® Filler CL particles appear to accumulate in skin structures like fine lines and wrinkles thus making their appearance less pronounced (Fig. 5). This effect is still observable 1 h after application.

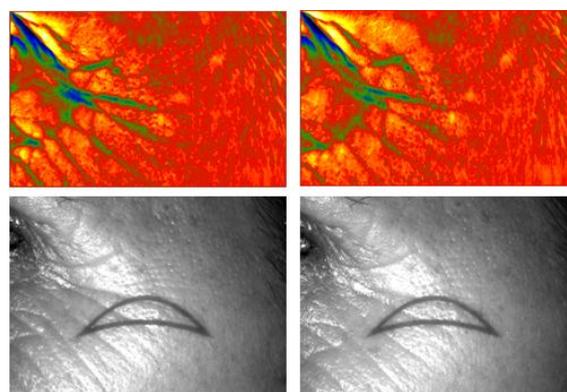


Fig. 5: PRIMOS Pico photos at start (left column) and 1 h after application (right column)

- **In vivo evaluation of HyaCare® Filler CL moisturization and skin smoothing properties**

Method: For this study 16 volunteers were recruited. On the inner forearm of the panellists 4 test fields (4 cm² each) were marked. On these fields, two test formulations were applied. These formulations were O/W creams containing either 0.1% HyaCare® or 2.5% HyaCare® Filler CL. Skin moisturization and the skin surface were evaluated before the application and 2 h after the application.

Before each measurement the panellists acclimatized for at least 15 min. at 21 – 22 °C and 55% relative humidity. Skin moisturization was measured using a Corneometer. For the evaluation of the skin surface, a special camera (Visioscan VC 98, Courage & Khazaka) was used. This camera possesses a black/white video sensor and a ring-shaped UV light source. The picture taken with this camera is converted into a digital signal with 256 grey levels. Via the grey level distribution, the software calculates a volume parameter which describes the volume necessary to fill the wrinkles. Skin surfaces with more wrinkles and wrinkles which are deeper will have a higher volume parameter.

Results: Corneometer readings show that 0.1% HyaCare® slightly improved skin moisturization with the effect lasting 2 h after application (Fig. 6). However, the results clearly also show the superior moisturizing properties of the formulation containing 2.5% HyaCare® Filler CL.

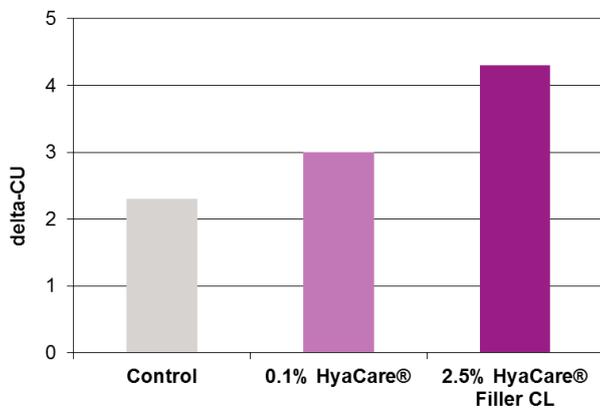


Fig. 6: Increase of Corneometer Units 2h after application

The effect of the two test formulations on appearance of wrinkle depth was markedly different. Two hours after application of the formulation containing HyaCare® Filler CL, a strong reduction of the skin volume was observed (Fig. 7). A reduction of the skin volume means that the apparent number and visible depth of wrinkles was reduced. This observation can be explained by the accumulation of HyaCare® Filler CL particles in fine lines shown in Fig. 5.

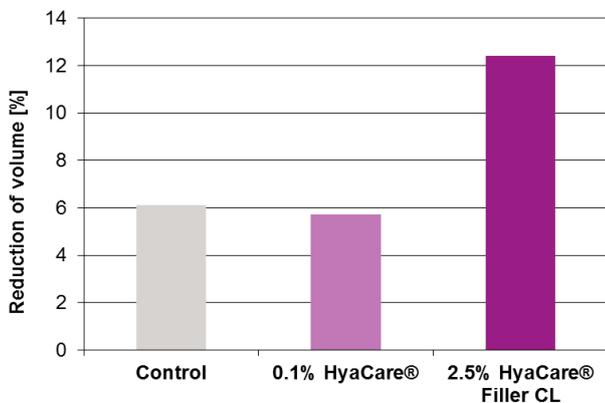


Fig. 7: Reduction of skin volume after the application of the test formulation

No such reduction was observed with the formulation containing HyaCare®.

- ***In vivo* evaluation “long” lasting wrinkle filling with HyaCare® Filler CL**

In addition to the short term effect, the “lasting” effect of apparent wrinkle reduction with HyaCare® Filler CL was analyzed. The ability of HyaCare® Filler CL to provide an apparently smoother skin surface was examined by comparing several concentrations of the cross-linked polymer.

Method: For this study, 11 volunteers were recruited. In summary, 18 test fields (5 cm² each) per formulation were analyzed. As test formulations, O/W creams containing 1.0%, 2.0% and 5.0% HyaCare® Filler CL were applied on the inner forearm. Skin surface and roughness parameters were evaluated with the Visioscan VC 98 camera before the application, 1 h, and 6 h after application. Before each measurement, the panelists acclimated for at least 15 min at 21 – 22 °C and 45–50% relative humidity.

Results: Analysis of the Visioscan images reveals significant improvement of skin surface smoothness and therefore, a decrease in apparent wrinkle depth after 1 h can be achieved with 1% HyaCare® Filler CL (Fig.8). The effect at higher concentrations is similar to that observed at 1%, at the first time point.

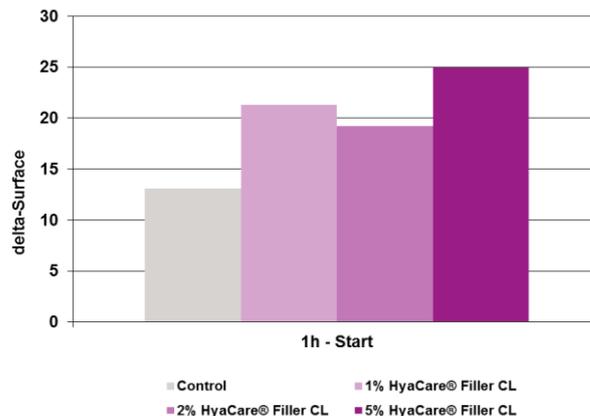


Fig. 8: Improvement of skin surface 1 h after application

The positive effect on skin roughness (reduction of apparent wrinkle depth) lasts for at least 6 h after application (Fig. 9).

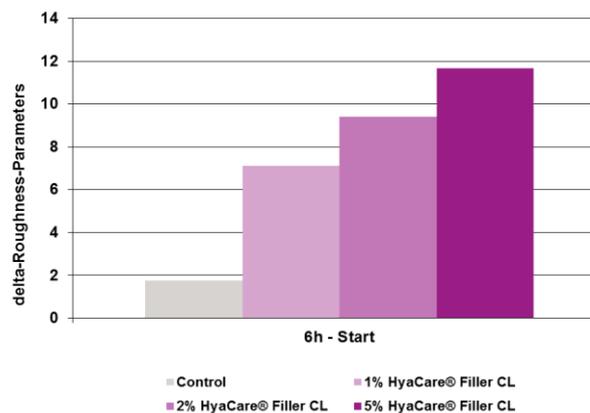


Fig. 9: Improvement of skin roughness (R1–R5) 6 h after application

To further demonstrate the effects observed on the forearms, an O/W cream containing 5% HyaCare® Filler CL was applied on the face. Images of forehead furrows were taken at 15 min. (Fig. 10) and 1 h (Fig. 11) after application. As can be clearly seen when comparing the images before product application (left panels) to those after application (right panels), there is a clear decrease in the

apparent depth and number of visible wrinkles at 15 min. after application.



Fig. 10: Application of an O/W cream containing 5% HyaCare® Filler CL (left side before application, right side 15 minutes after application)

The effect is still visible 1 h after product application, confirming the results observed on the forearms.

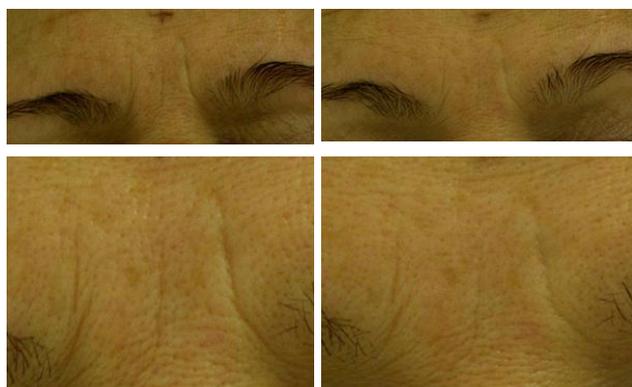


Fig.11: Application of an O/W cream containing 5% HyaCare® Filler CL (left side before application, right side one hour after application)

Conclusion

HyaCare® Filler CL possesses strong moisturizing properties due to the strong water absorbing properties of the cross-linked Hyaluronic Acid. Therefore, it is able to act as topical dermal filler, quickly reducing the appearance of wrinkles after application. This makes it especially suitable for day creams, eye creams or color formulations, like make-up, foundation and lip sticks, claiming an immediate wrinkle reducing effect.

Preparation

• Preparation of an O/W-Emulsion (Cream or Lotion):

Normally HyaCare® Filler CL should be added to the oil phase of the emulsion. Then the emulsion is prepared as usual.

In some cases HyaCare® Filler CL might disturb the build up of the liquid crystalline structure of the O/W-emulsion. In these cases, it is recommended to add it during the cooling process at temperatures below 40 °C.

If high concentrations of HyaCare® Filler CL are used (4 - 5%), it increases the viscosity of the O/W emulsion. In this case, the viscosity can be adjusted by decreasing the concentration of consistency enhancers like fatty alcohols (TEGO® Alkanol 16, 1618 or 18) and glyceryl stearate (TEGIN® M Pellets).

• Preparation of a W/O-Emulsion (Cream or Lotion):

The W/O emulsion is prepared as usual. At the end of the production HyaCare® Filler CL is added.

Recommended usage concentration

0.5 - 5% of HyaCare® Filler CL

Patent position

The production and cosmetic use of HyaCare® Filler CL is subject of patent application WO2009077399 (crosslinked hyaluronic acid in emulsion). To the best of our knowledge no third party patent right exists that prevents customers from using HyaCare® Filler CL in cosmetic formulations.

Applications

- Anti-wrinkle eye care products
- Anti-aging facial serum
- Special care for expression lines
- Skin plumping face care
- Facial sun care
- Intense moisturizing skin care
- Wrinkle reducing foundations

Packaging

5 kg package

Hazardous goods classification

Information concerning

- classification and labelling according to regulations for transport and for dangerous substances
- protective measures for storage and handling
- measures in accidents and fires
- toxicity and ecological effects

is given in our material safety data sheets.

Guide Line Formulations

| Wrinkle Smoothing Eye Cream MAC 672/1/1 | |
|--|-------------|
| Phase A | |
| TEGO [®] Care 450 (Polyglyceryl-3 Methylglucose Distearate) | 3.0% |
| TEGIN [®] M Pellets (Glyceryl Stearate) | 2.0% |
| TEGO [®] Alkanol 18 (Stearyl Alcohol) | 2.0% |
| TEGOSOFT [®] CT (Caprylic/Capric Triglyceride) | 7.5% |
| TEGOSOFT [®] DC (Decyl Cocoate) | 9.5% |
| Avocado Oil | 2.0% |
| Tocopheryl Acetate | 0.5% |
| HyaCare[®] Filler CL | 3.0% |
| Phase B | |
| Glycerin | 3.0% |
| Water | 67.5% |
| Phase C | |
| Lactic Acid (10%) | q.s. |
| Phase Z | |
| Preservative, Parfum | q.s. |
| Preparation: | |
| <ol style="list-style-type: none"> 1. Heat phase A and B to approx. 80 °C. 2. Add phase A to B while stirring.¹⁾ 3. Homogenize. 4. Cool down to 30 °C. Add phase C and Z below 40 °C. | |
| ¹⁾ Important: If phase A has to be charged into the vessel first, add phase B without stirring. | |

| Dermal Filler Cream MAC 672/3/1 | |
|--|-------------|
| Phase A | |
| Axol [®] C62 Pellets (Glyceryl Stearate Citrate) | 1.5% |
| TEGIN [®] M Pellets (Glyceryl Stearate) | 3.0% |
| TEGO [®] Alkanol 18 (Stearyl Alcohol) | 2.0% |
| Stearic Acid | 1.0% |
| TEGOSOFT [®] CT (Caprylic/Capric Triglyceride) | 8.5% |
| TEGOSOFT [®] M (Isopropyl Myristate) | 7.0% |
| TEGOSOFT [®] CR (Cetyl Ricinoleate) | 2.0% |
| HyaCare[®] Filler CL | 3.0% |
| Phase B | |
| Glycerin | 3.0% |
| Water | 68.0% |
| Phase C | |
| TEGO [®] Carbomer 134 (Carbomer) | 0.2% |
| TEGOSOFT [®] CT (Caprylic/Capric Triglyceride) | 0.8% |
| Phase D | |
| Sodium Hydroxide (10% in water) | q.s. |
| Phase Z | |
| Preservative, Parfum | q.s. |
| Preparation: | |
| <ol style="list-style-type: none"> 1. Heat phase A and B to approx. 80 °C. 2. Add phase A to B with stirring.¹⁾ 3. Homogenize. 4. Cool down to 60 °C and add phase C. 5. Homogenize again for a short time. 6. Cool down to 30 °C. Add phase D and Z below 40 °C. | |
| ¹⁾ Important: If phase A has to be charged into the vessel first, add phase B without stirring. | |

| Dual-Action Wrinkle Serum | | | |
|---|-----|------|-------------|
| MK 3/10-25 | | | |
| Phase A | | | |
| ABIL® | EM | 90 | 1.5% |
| (Cetyl PEG/PPG-10/1 Dimethicone) | | | |
| ABIL® | EM | 97 | S 1.0% |
| (Bis-PEG/PPG-14/14 Dimethicone; Dimethicone) | | | |
| Cyclopentasiloxane | | | 12.0% |
| TEGOSOFT® DEC (Diethylhexyl Carbonate) | | | 3.0% |
| HyaCare® Filler CL | | | 2.5% |
| Tocopherol | | | 0.5% |
| Zinc Stearate | | | 0.5% |
| Phase B | | | |
| Water | | | 69.7% |
| Glycerin | | | 4.0% |
| Butylene Glycol | | | 4.0% |
| Sodium Chloride | | | 0.8% |
| TEGO® | Pep | 4-17 | 0.5% |
| (Tetrapeptide-21; Glycerin; Butylene Glycol; Aqua) | | | |
| Phase Z | | | |
| Preservative, Parfum | | | q.s. |
| Preparation: | | | |
| <ol style="list-style-type: none"> 1. Heat phase A to approx. 80 °C. 2. Add phase B (80 °C or room temperature) slowly while stirring. 3. Homogenize for a short time. 4. Cool with gentle stirring below 30 °C and homogenize again. | | | |

| Anti-Aging Foundation | | | |
|--|-----|------|--------------|
| DCA-5787-200 | | | |
| Phase A | | | |
| ABIL® | EM | 180 | 3.00% |
| (Cetyl PEG/PPG-10/1 Dimethicone) | | | |
| TEGOSOFT® APM (PPG3-Myristyl Ether) | | | 5.00% |
| TEGOSOFT® TN (C12-15 Alkyl Benzoate) | | | 5.00% |
| TEGOSOFT® DEC (Diethylhexyl Carbonate) | | | 10.00% |
| Phytosphingosine | | | 0.05% |
| Talc | | | 1.60% |
| Titanium Dioxide (BTD-11S2, Kobo) | | | 5.00% |
| Iron Oxide | | | 1.90% |
| Phase B | | | |
| Water | | | 59.55% |
| HyaCare® 50 (Hydrolyzed Hyaluronic Acid) | | | 0.10% |
| TEGO® | Pep | 4-17 | 3.00% |
| (Tetrapeptide-21; Glycerin; Butylene Glycol; Aqua) | | | |
| Propylene Glycol | | | 2.00% |
| Sodium Chloride | | | 0.80% |
| Phase C | | | |
| HyaCare® Filler CL | | | 3.00% |
| Phase Z | | | |
| Preservative, Parfum | | | q.s. |
| Preparation: | | | |
| <ol style="list-style-type: none"> 1. Mix the ingredients of phase A and ensure the proper dispersion of the pigments. 2. Mix the ingredients of phase B. 3. Add phase B slowly to phase A while stirring. 4. Homogenize. 5. Add phase C and stir until it is homogenous. | | | |

| Caring Lip Balm CC004-0007 | |
|---|--------|
| Phase A | |
| HyaCare® Filler CL (Aqua; Ethylhexyl Stearate; Sodium Hyaluronate Crosspolymer; Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate; Sodium Isostearate) | 5.00% |
| ISOLAN® GPS (Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate) | 0.5% |
| Phase B | |
| TEGOSOFT® G 20 (Octyldodecanol) | 22.60% |
| TEGOSOFT® CT (Caprylic/Capric Triglyceride) | 18.00% |
| TEGOSOFT® SH (Stearyl Heptanoate) | 7.70% |
| TEGOSOFT® MM (Myristyl Myristate) | 4.40% |
| TEGO® Alkanol 1618 (Cetearyl Alcohol) | 2.20% |
| Microcrystalline Wax | 21.50% |
| Ricinus Communis (Castor) Seed Oil | 10.40% |
| Copernicia Cerifera (Carnauba) Wax | 1.30% |
| Butyrospermum Parkii (Shea) Butter | 1.00% |
| Simmondsia Chinensis (Jojoba) Seed Oil | 1.00% |
| Beeswax | 0.55% |
| Ethylhexyl Methoxycinnamate | 3.30% |
| Butyl Methoxydibenzoylmethane | 0.55% |
| Preparation: | |
| <ol style="list-style-type: none"> 1. Heat phase B to 85 °C. 2. Add phase A into Phase B at 85 °C. 3. Mould the mixture at 85 °C. 4. Cool down the mould to -15 °C after moulding and stay for 15-35 minutes. 5. Demould and pack. | |

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(Status: April, 2008)