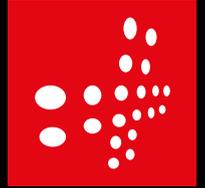
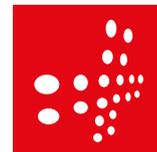


CONTRAD  
S W I S S



**SIGMOLECS®**  
**AND ACTV8SKN®:**  
**CLINICAL RESULTS**



## **SIGMOLECS® AND THE ACTUATOR**

The appearance of the skin is the hallmark of beauty. The complexion is the first indicator that broadcasts a person's state of wellbeing. This perception has become a global focus, motivating people to employ anti-age products, both OTC and clinical. Preventive cosmetology and quick-fix reparative strategies have crossed the chasm of vanity to become an essential health service for wellbeing.

Today, rejuvenating therapies are available to everyone. Aesthetic medicine has advanced to provide different therapies that range in intensity and cost, enabling anyone to afford aesthetic treatment.

From dermabrasion to micro-needling to PRP; aesthetic medicine has joined the ranks of high-tech procedures using super technical devices and clinical protocols to adjust, refine and regenerate beauty.

CONTRAD leads the way in the development of innovative products that support clinical aesthetic medicine. Their products are clinically applicable as adjuvants to therapy in regenerative techniques such as PRP. They can enhance the outcome of procedures, cut-down recovery time, and sustain clinical rejuvenating treatments.

## **WHAT ARE ANTI-AGING PRODUCTS?**

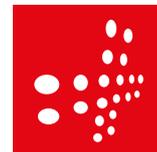
Topical anti-aging products are basically divided into two categories:

1. Antioxidants; which comprise creams formulated with vitamins and phytochemicals like flavonoids and polyphenols that quench free radicals.
2. Cell regulators; which are formulated with proteins and peptides such as growth factors and signaling molecules to have a direct effect on the pathophysiological processes of aging; such as restoring extracellular matrix scaffolds, laying-down of collagen and improving cellular function of skin fibroblasts and keratinocyte turnover in aging patients.

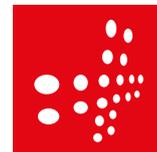
CONTRAD focuses on cell regulation through its state-of-the-art technology: SIGMOLECS®.

SIGMOLECS® contains peptides with signaling sequences designed specifically for aesthetic purposes and their cellular pathways targeted in clinical procedures. At the same time, the technology provides a medium for these molecules to interact with the subcellular levels of the skin that stimulate endogenous antioxidant defenses.

Oligopeptides are notorious for their compatibility with the skin, similar to many cosmeceutical -vitamins, and components like retinoids, which cause dryness and irritation, especially when used with light devices and lasers. Furthermore, retinoid side-effects are exacerbated by sun exposure, making them inconvenient for most patients. The ACTUATOR is free of any of these components and as such is a highly compatible product for clinical application and post-clinical use.



KEY INGREDIENT	GENERAL ACTION	SPECIFIC ACTION BY SIGMOLECS® BIOMIMETIC ACTUATED PEPTIDES IN ACTV8SKN®
<b>SH-OLIGOPEPTIDE-1</b>	<p>A synthesized peptide that codes for human epidermal growth factor (EGF); structured to emulate intracellular signaling by EGF related to dermal repair and regeneration. Specifically, this ingredient stimulates epithelial and endothelial cells and fibroblast that are called to repair pathways by skin and immune cells. It is highly involved in regulating blood flow and repairing wounds. It is stimulated by the inflammatory response to infiltrate the site of wounds and induce repair of the dermal structures and their vasculature quickly and without scarring.</p>	<p>SIGMOLECS® SH-OLIGOPEPTIDE-1 is specifically structured into an advanced biomimetic profile to mimic EGF isomers which when applied:</p> <ul style="list-style-type: none"> <li>• Improves skin texture, pore size and clarity, thus erasing the visible signs of aging.</li> <li>• Improves circulation and antimicrobial and antioxidant action.</li> <li>• Restores skin texture and erases staining from blood pooling due to metabolic disorders, drugs and aging.</li> <li>• Restores circulatory oxygenation and stimulates neo-epithelial cells which adds luminescence to skin tone, leaving a younger looking complexion.</li> <li>• Resurfaces skin over time, which can treat pits and scars and other surface imperfections.</li> </ul>
<b>SH-OLIGOPEPTIDE-2</b>	<p>A synthesized peptide that codes for human insulin-like growth factor (IGF); structured to emulate intracellular signaling by IGF related to connective tissue. Specifically, this ingredient offers substantial protection to keratinocytes and dermal fibroblasts. It can easily penetrate the epidermis to induce fibroblast-mediated responses in the dermis. It inhibits acetylcholine receptor release, thereby protecting fibroblasts from oxidative stress, particularly stress induced by ultraviolet (UV) damage. It is involved in connective tissue pathways and protects vascular walls against oxidation.</p>	<p>SIGMOLECS® SH-OLIGOPEPTIDE-2 is specifically structured into an advanced biomimetic profile to mimic certain IGF isomers which when applied:</p> <ul style="list-style-type: none"> <li>• Protects skin cells against environmental pollutants and UV exposure and damage;</li> <li>• Controls blood pools that can result in staining; such as dark circles under the eyes and hemosiderin staining;</li> <li>• Protects dermal vasculature from UV damage and oxidative stress;</li> <li>• Prevents aging by restoring IGF pathways.</li> </ul>
<b>SH-POLYPEPTIDE-1</b>	<p>A synthesized peptide that codes for human fibroblast growth factor (FGF); structured to emulate intracellular signaling by FGF related to dermal integrity, collagen scaffolding and inhibition of oxidative stress pathophysiology. Specifically, this ingredient increases the area and number of neo-epithelia and capillary formation. Mediates signaling of protein Akt, preventing development of stressed collagen fibers; this translates to protection against UV damage and the development of skin cancer.</p> <p>Mediates Rho-associated kinases, the intracellular kinases that bind proteins to form stress fibers and myofibroblasts, thereby inhibiting myoblastic collagen formation that leads to scarring and skin thickening. It accentuates the action of hyaluronic acid and stimulates its innate production.</p>	<p>SIGMOLECS® SH-POLYPEPTIDE-1 is specifically structured into an advanced biomimetic profile to mimic certain FGF isomers which when applied:</p> <ul style="list-style-type: none"> <li>• Prevents skin thickening due to oxidative stress, pollution and sun and wind damage,</li> <li>• Stimulates regeneration of skin cells and good collagen production.</li> <li>• Improves skin's elasticity overall.</li> <li>• Protects and preserves intact epidermis and dermis and regulates synthesis of new blood vessels, improving and maintaining tissue viability.</li> <li>• Prevents scarring during healing and following procedures.</li> </ul>
<b>SH-POLYPEPTIDE-42</b>	<p>A synthesized peptide that codes for interleukin-7 (IL-7); structured to emulate intracellular signaling by IL-7 related to cell differentiation and homing. Specifically, this ingredient regulates cell growth ensuring proper differentiation, and activating homing responses of responses of new cells. It prevents cellular apoptosis. Stimulates several immune responses in multiple cell types and regulates hormonal influences.</p>	<p>SIGMOLECS® SH-POLYPEPTIDE-42 is specifically structured into an advanced profile in order for it to mirror certain IL-7 isomers which when applied:</p> <ul style="list-style-type: none"> <li>• Is highly anti-aging and rejuvenating; favoring skin cell renewal.</li> <li>• Prevents inflammation due to environmental injury as well as metabolic conditions, thus increases immune tolerance of skin cells. Within the ACTV8SKN® combination this contributes an effect similar to stem cells in renewing the dermis.</li> </ul>



SIGMOLECS® molecules within ACTV8SKN® induce dynamic bioactivity and signaling properties.

As a general daily cosmetic, ACTV8SKN® signals promoter regions for glycosaminoglycan synthesis within the connective tissue, which in this case, gives a cumulative effect of collagen and elastin regeneration. This means that ACTV8SKN® has sustained cosmetic action. It gives you instant effect, but its continued use supplements the regenerative powers of your skin cells.

The combination and assembly of SIGMOLECS® actuated molecules launches signals that mediate many skin responses to environmental injury and aging. For example, our proprietary combination in ACTV8SKN® inhibits aging-related receptors thus contributing protective armor to keratinocytes against skin aging due to DNA damage from neuronal stress, immune dysfunction, and oxidative radicals. At the same time, it governs endocrine and immune modulation.

For example, one of ACTV8SKN® SIGMOLECS® actuated molecules mimics  $\alpha 7$  nicotinic acetylcholine receptor agonist tropisetron, which protects against ultraviolet mediated oxidative stress in human fibroblasts, therefore minimizing the effects of sun damage such as wrinkling, as well as other atopic diseases related to ultraviolet breakdown and damage of skin cells. At the same time, it is anti-inflammatory and protective against other detrimental pathways to skin cells that tend to induce inflammation.

## **OVERALL PROPERTIES OF THE ACTUATOR AS A DAILY COSMETIC**

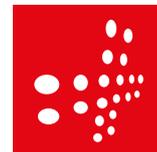
Promotes specific types of collagen synthesis through peptide signaling.

Stimulates synthesis of hyaluronic acid and glycoproteins.

Inhibits aging and wrinkling pathways by inhibiting certain receptors; such as acetylcholine receptor release.

Inhibits release and subsequent activation of inflammatory cytokine pathways esp. interleukin-1, 6 and 8, thereby protecting against oxidative stress.

Prevents free carbonylation within the formula and from skin cells. This means that it prevents environmental gases such as carbon monoxide and other industrial pollutants from oxidizing the proteins in the formulation, and therefore by using the ACTV8SKN® formula, provides the same protection against contamination and injury to skin cells.



## THE ACTUATOR STUDY

A clinical study was conducted on the SIGMOLECS® cosmetic ACTV8SKN® to evaluate its brightening, moisturizing and viscoelastic-restorative effects.

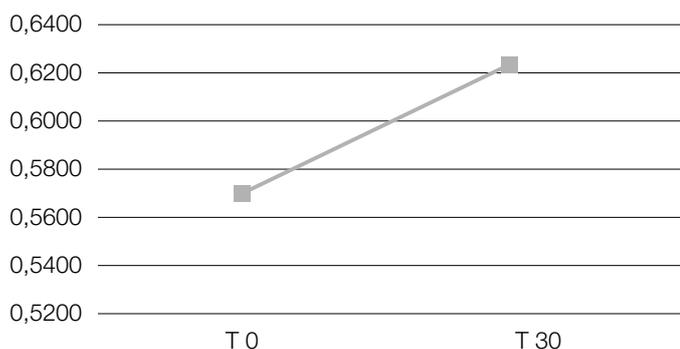
The study, performed by a third party GLP-testing facility applied ACTV8SKN® on 20 female volunteers between the ages of 35-55, for a period of 30 days.

## Summary of Results

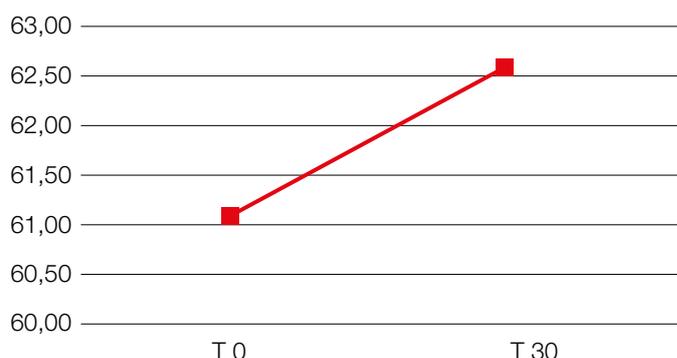
- 11.80% increase in elasticity within 30 days
- 6.32% decrease in skin tiring effect
- 2.45% improved complexion from “bright” to “very bright” per individual
- 14.37% ‘real time’ increase in skin hydration
- 100% NOAEL (non observed adverse effect level)

Throughout the entire study, none of the volunteers experienced any adverse reactions such as skin irritation, burning, redness or itching.

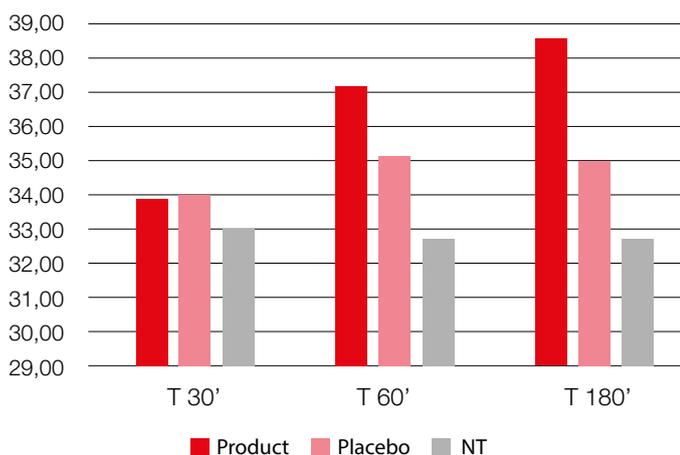
MEAN R2 - ELASTICITY



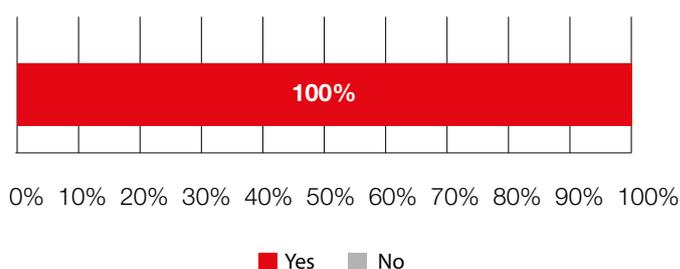
L\* MEAN VALUE

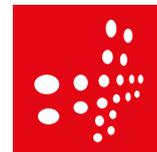


MEAN HYDRATION



NOAEL = 100%





## SAFETY ASSESSMENT OF THE ACTUATOR

### MARGIN of SAFETY (MoS)

Dermal absorption and frequency of application and exposure assessment are criteria to evaluate the margin of safety (MoS). For the purpose of clinical application within aesthetic medical procedures, skin thickness has been considered to determine dermal absorption values for both dermal absorption per application and per peptide complex.

The MoS for average application as an OTC product (applied as a general cosmetic over the entire face) using default values of skin surface area in an adult female face (1600 cm<sup>2</sup>) yielded an MoS of 188.

Thickness values from the Actuator clinical study, for pinpoint zones tested, yielded an average MoS = 200. These values are significantly above the 100-value mark of a MoS considered safe for continued exposure/application, even in children and infants.

The following table illustrates MoS values for specific epidermal + dermal skin thicknesses commonly targeted in aesthetic medicine.

The MoS values on all zones are well above the 100-value mark; considered by CFDA and EU Cosmetic Guidelines to be 'safe' and 'applicable to children' as well. This characterizes the Actuator as a non-toxic product. Moreover, the clinical study yielded a 100% NOAEL from volunteers, with a b.i.d exposure dosage (application) over a 30 day period.

Furthermore, the SIGMOLECS® technology synthesizes peptides in solution through a proprietary process and sequencing technique, so there is no reconstitution with solvents; therefore, there is no risk of solvent contamination in the final product.

Throughout the entire study, none of the volunteers experienced any adverse reactions such as skin irritation, burning, redness or itching.

FACIAL ZONE	average EPIDERMAL THICKNESS (µm)	average DERMAL THICKNESS (µm)	Standard deviation	MoS	SED (Exposure Dosage)
Upper medial forehead	44.70	1200.93	297.23	240.96	4.15
Lower medial forehead	45.76	1176.11	342.84	245.70	4.07
Upper lateral forehead	44.80	1252.50	566.26	231.48	4.32
Lower lateral forehead	39.86	1172.34	541.04	247.52	4.04
upper medial eyelid	40.31	758.85	444.91	375.93	2.66
Lower medial eyelid	48.01	868.39	457.37	327.87	3.05
Upper lateral eyelid	42.39	1088.58	528.57	265.25	3.77
Lower lateral eyelid	38.58	1227.10	780.79	236.97	4.22
Tear trough	47.00	1178.64	704.89	245.10	4.08
Glabella	46.59	1339.52	466.82	216.45	4.62
Malar	45.73	1040.46	408.69	276.24	3.62
Lower cheek	44.66	1291.26	427.13	224.72	4.45
Nasolabial fold	48.91	1250.18	607.87	230.95	4.33
Marionette fold	40.87	989.41	588.19	291.54	3.43
Anterior neck	40.69	1237.68	555.27	234.74	4.26
Lateral neck	32.89	1440.71	623.97	203.66	4.91

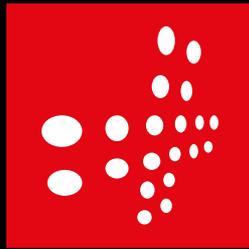
*Skin Thickness Values referenced from 'The Aesthetic Surgery Journal 2015, Vol 35(8)1007-1013.*

*Risk assessment calculations according to Cosmetic Safety Risk Assessment guidelines.*

### REFERENCE GUIDELINES

*All calculations and values are according to the CFDA guidelines; FDA cosmetic safety evaluation guidelines as well as the EU Cosmetics Directive (76/768/EEC) and toxicological data requirements for cosmetic ingredients based on SCCNFP guidelines.*

*Dose response assessment, NOAEL (non observed adverse effect level), risk characterization (MoS) all conform to both FDA and EU Cosmetic Directive guidelines.*



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