AZELOGLICINA®

MULTIFUNCTIONAL INGREDIENT FOR ADVANCED SKIN CARE

Sinerga
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summary

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AZELOGLICINA®

AZELAIC ACID

insoluble in water

SKIN LIGHTENER
SEBUM NORMALIZER

GLYCINE

soluble in water

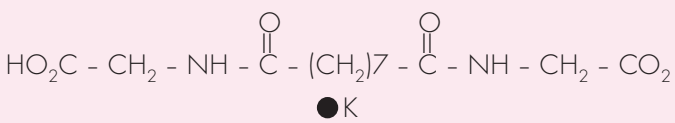
HYDRATING AGENT

AZELOGLICINA® is the condensation product between one mole of Azelaic Acid and two moles of Glycine. This new molecule is an improvement upon the individual properties of Azelaic Acid and Glycine. (Patent Sinerga)

AZELOGLICINA®

SKIN LIGHTENING
SEBUM NORMALIZING
HYDRATING
ELASTICIZING

The chemical modification from Azelaic Acid to AZELOGLICINA® has led to an equally active ingredient, but much improved from a technical point of view. Indeed, **Potassium Azeloyl Diglycinate** (Trade Name: AZELOGLICINA®) is a water soluble derivative of Azelaic Acid, maintaining all the cosmetic properties of the original molecule, but improving its technical characteristics.



Potassium Azeloyl Diglycinate

product CHARACTERISTICS

AZELOGLICINA®

- multifunctional ingredient
- compatible with usual cosmetic ingredients
- completely soluble in water
- stable in the pH range from 5 to 11
- non-irritating to skin and mucosa
- self-preserving

Applications

AZELOGLICINA®
multi functional ingredient

skin lightening: in formulations for lightening dark skin or for skin pigmented melaninic spots

sebum normalizing: a functional ingredient for formulations intended to regulate sebum

hydrating and elasticizing: in formulations for dehydrated skin.

APPLICATION:
AZELOGLICINA®
is used in aqueous systems such as cleansers, clear solutions, gels, gel-emulsions and both low and high viscosity O/W emulsions.

It is not suitable for W/O emulsions or for anhydrous systems.

Suggested dosage:
from 3% to 10%

Physical-Chemical *data*

Chemical Name	Glycine,N,N'-(1,9-dioxo-1,9-nonanedyl (bis-,monopotassium salt)
INCI Name	Potassium Azeloyl Diglycinate
CAS N°	477773-67-4
JCIA Approval	n° 4874
Appearance	Clear liquid
Color	Colorless to light yellow
Odor	Odorless

Density (25°C)	1.135 - 1.145
pH	7.0 - 8.0
Dry Residual	30 - 32%
Molecular Weight	344
Molecular Formula	$C_{13}H_{22}N_2O_6$
Solubility	Completely soluble in water

Efficacy evaluations

In order to prove the effectiveness of the product, several efficacy evaluation have been carried on human volunteers

lightening efficacy

on caucasian skin types

Aim of this test is to evaluate the whitening efficacy of AZELOGLICINA® on both hyperchromic and spotless skin areas. The product, in the form of a 3% aqueous solution, was applied on 5 volunteers having hypermelanic spots. Each subject applies the product on the back of one hand twice a day for three weeks.
At the beginning and after the three weeks' treatment skin colour was measured by a Minolta Colorimeter (Chroma meter CR 300) on the following areas:

- on the chosen hypermelanic spot (treated spot)
- on the skin area of the hand treated with the product and without hypermelanic spots (treated skin)
- on an hypermelanic spot on the untreated hand (untreated spot)
- a skin area of the untreated hand (untreated skin)

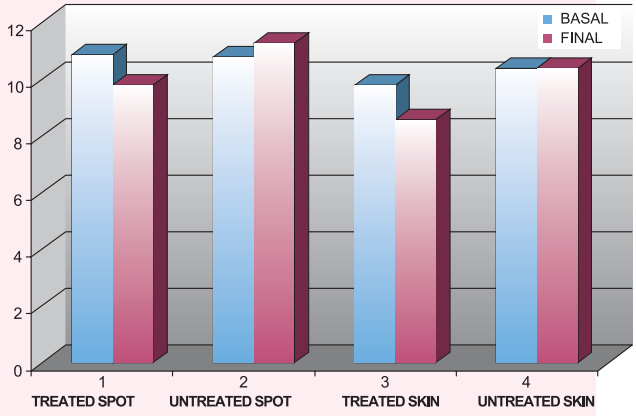
The parameters evaluated were: "L" (luminosity), "a" (red-green axis), "b" (yellow-blue axis), that together define skin colour. As internal reference, non treated sites were controlled at the beginning and at the end of treatment.

RESULTS
"L" parameter reveal a significant increase in skin brightness on both areas treated with the product. The whitening efficacy of the product was also confirmed by a decrease in skin colour, concerning parameter "a" and "b" .

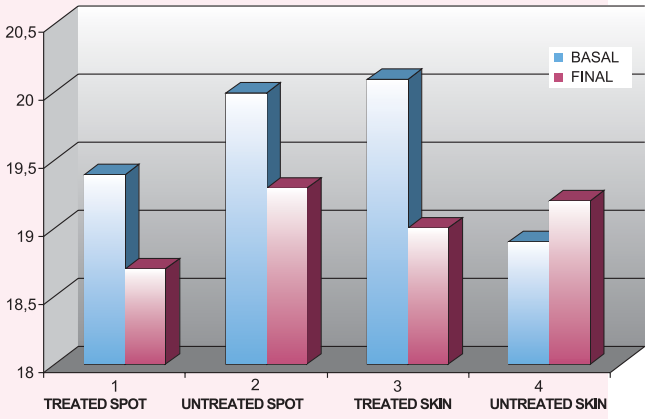
Following the results are represented in a summarizing table.

L*	On pigmented skin +3.2% related to the control +1.6% On normal skin +5.4% related to the control –0.9%
a*	On pigmented skin – 10.1% related to the control +4.6% On normal skin – 12.2% related to the control 0%
b*	On pigmented skin -3.6% related to the control +3.5% On normal skin -5.5% related to the control – 1.6%

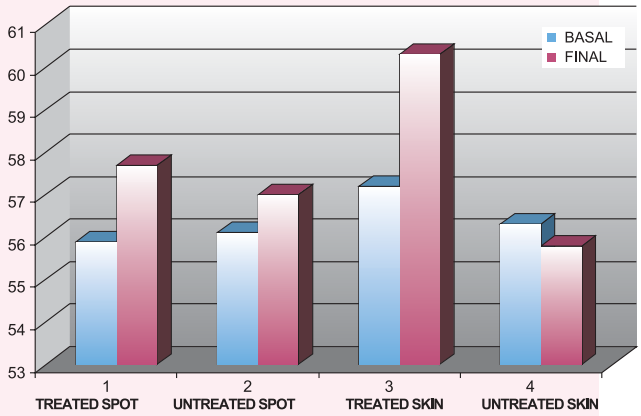
CUTANEOUS COLORIMETRY: VALUE a*- RED - GREEN AXIS



CUTANEOUS COLORIMETRY: VALUE b*- YELLOW - BLUE AXIS



CUTANEOUS COLORIMETRY: VALUE L*- BRIGHTNESS



whitening efficacy

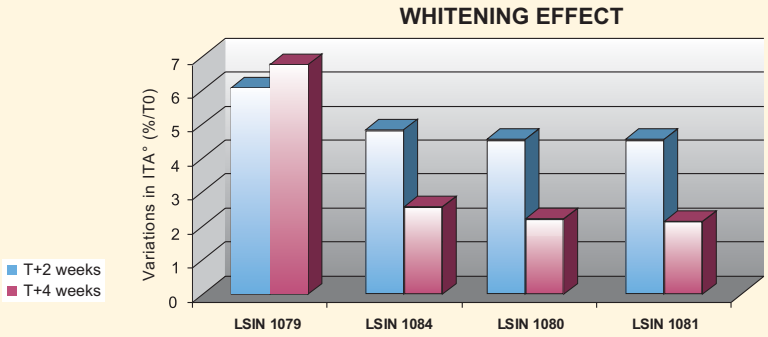
on asian skin types

The objective of this study will be the evaluation and the comparison of the in vivo effects of 4 whitening products on 40 healthy Asian female subjects between 18-40 years of age, with skin phototypes III or IV
This will be a randomized double-blind study. Subjects will be allocated to groups and treatments assigned using a scheme that maintains balance for both of the above named randomization factors. This study will be conducted with 2 groups as follows:

- Group 1: Product **LSIN 1079 (placebo)** versus Product **LSIN 1084 (AZELOGLICINA® 5%)**;
- Group 2: Product **LSIN 1080 (Kojic acid dipalmitate)** versus Product **LSIN 1081 (Arbutin)**.

Each product will be applied on one randomized half-face twice daily over a 4 week-period, by the subjects themselves.
Measurements of skin's color on the measuring site (1 site per treated half-face) has been performed using the chromameter Minolta CR-300.
The different measurements will be done on the face and neck for each subject, on sites defined using a gabarit.
Measurements will be performed throughout the study on the treated and control sites (at T0, T+2, and T+4 weeks), and mean values from 5 successive measurements will be calculated.
Then the following parameters: ΔL*, Δa*, Δb*, and ΔITA° will be calculated between T0 and each of the following time points.
All these parameters will be determined for the two measured sides of the face and for the control site.

RESULTS
For evaluation of a whitening effect, we base our interpretation on 2 parameters (luminance L* and Individual Typological Angle ITA°, expression of skin pigmentation and Melanin index).
In our study, all the products tested have exhibited a whitening effect. This effect was significant at T+2 weeks for the products LSIN 1079 (placebo) and LSIN 1084 (AZELOGLICINA®), and significant at T+4 weeks.
Results are summerised in figure and table below.
These results seems to confirm the efficacy of the new compound AZELOGLICINA® on asian skin types for all comparable to other competitors, even better in times for effectiveness.
The tendency in decreasing b* parameter, already noticed in Caucasian skin types has been confirmed.



2 weeks	LSIN 1080	LSIN1081	LSIN 1084
L*	+ 0.7%	+0.5%	+0.9% (p<0.05)
a*	+ 1.1%	+2.9%	-3.8%
B*	0.0%	-1.0%	+0.6%
ITA°	+ 5.2%	+4.7%	+5.3% (p<0.05)

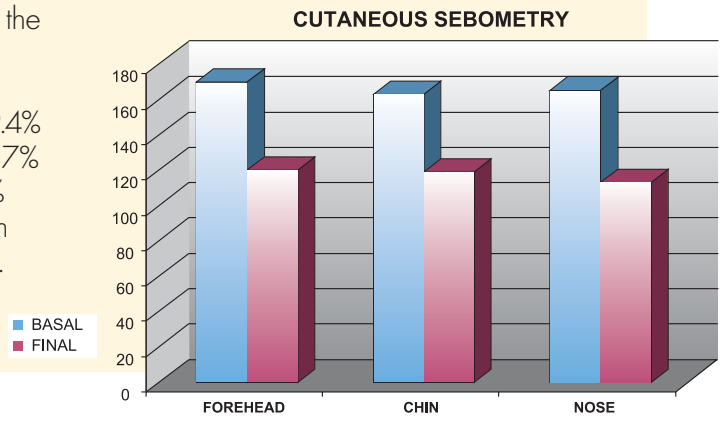
4 weeks	LSIN 1080	LSIN1081	LSIN 1084
L*	+ 0.4%	+0.3%	+0.4%
a*	+ 3.2%	+2.8%	+ 2.2%
B*	+ 0.4%	+0.2%	-0.1%
ITA°	+.2.5%	+2.3%	+3.6%

sebum normalizing efficacy

AZELOGLICINA® is effective in the treatment of oily and acneic skin, effectively reducing the excess of cutaneous lipids At the end of the treatment, the following decrease in cutaneous lipids were observed:

- on forehead: reduction of the initial values of 29.4%
- on nose: reduction of the initial values of 27%
- on chin: reduction of initial values of 31.5%

AZELOGLICINA® shows a significant sebum normalizing effect on the forehead and chin.



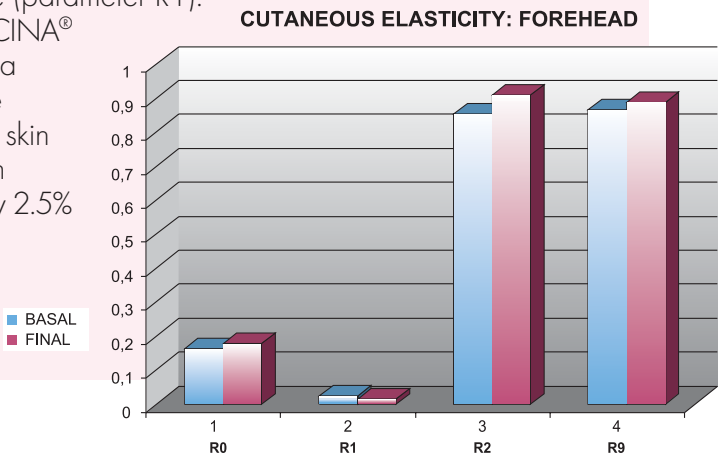
elasticizing efficacy

On the same volunteers, elasticity parameters were measured by means of a Cutometer. Three measurement cycles were performed: (1cycle: skin aspiration/release) on the same point. By way of the attached computer three curves are recorded that show the heights reached by the skin during the aspiration and the different levels of "release" of the skin during the release times.

FOREHEAD
The product produced a statistically significant increase in the skin elasticity (parameter R9) which is the parameter more directly corresponding to the improvement of the elastic features of the skin. This, in turn corresponds to the average between the elasticity values of the first and third curve. Even the maximum extendibility (parameter RO) increased after the use of the product, although not statistically significant, the skin release (parameter R1). AZELOGLICINA® performed a significative increase of skin elasticity on forehead by 2.5%

A potential increase of skin elasticity of the first curve was noticed (parameter R2).

This parameter represents the ratio between the skin release and the maximum extension of the first curve.

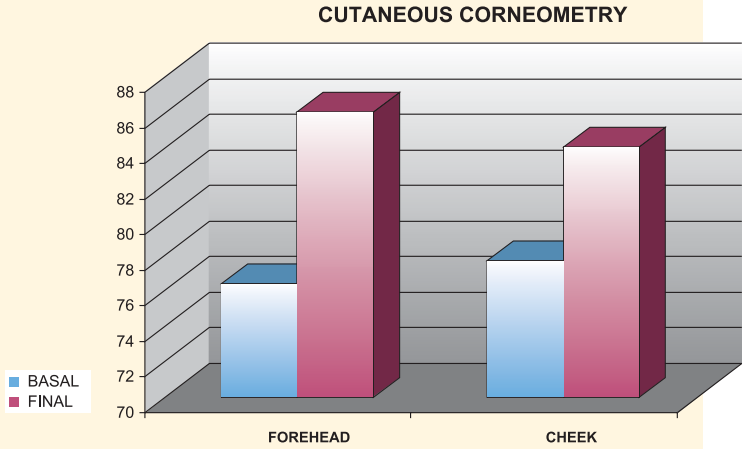


hydrating efficacy

The same product (3% aqueous solution) was applied on volunteers' skin having low skin hydration as measured with a Corneometer. The product was applied on the face twice a day for three weeks.
Instrumental measurements of hydration and elasticity were performed at the beginning and at the end of the treatment period.
The micro-structure of the stratum corneum was evaluated, in vivo, through a plastic replica imaging technique of the skin surface.
Measurements were carried out on two different areas of the face: the forehead and the cheek. The data were statistically analyzed and compared.

Results show a statistically significant increase in the basal value of skin hydration on both selected areas of skin.

AZELOGLICINA® led to an increase in the basal value of skin moisture in both considered areas:
- forehead: moisture increased by 12.7%
- cheek: moisture increased by 8.2%



Interest for
DERMATOLOGISTS

Azelaic Acid

Azelaic acid is widely know for its antibacterial, sebum-normalizing and keratoplastic capabilities and is normally used in 15-20% concentrations; it may cause, as a consequence of its activity on sebum reduction and modulation of skin proliferation, skin dryness and irritation.

Azelaic acid is produced by the microrganism *Pityrosporum ovale* (and other species), which is responsible for the cutaneous disease known as "pitiryasis vescicolor". This microrganism causes leucodermic spots on which melanin is not present. Its mechanism of action has been proved as a **competitive inhibition of Tyrosinase**, the main enzyme involved in the formation of melanin. From this evidence, *Azelaic Acid* has been topically used in the dermatologic treatment of hypermelanic spots. Another important application of Azelaic Acid in dermatology is due to its bacteriostatic activity: azelaic acid has bacteriostatic properties versus aerobic and anaerobic. This activity is probably due to the inhibition of cells' proteic synthesis, while it also performs a reduction of free fatty acids in cutaneous sebum due to a **competitive inhibition of the enzyme 5-α reductase**.

Azelaic Acid presents some technical and formulating problems. In fact, it is not water soluble, giving poor cosmetic properties to formulations, thus resulting thick and difficult to spread. Furthermore, it has a quite a high melting temperature for cosmetic ingredients (105-106°C), making azelaic acid quite difficult to handle in standard conditions.

DERMATOLOGICAL USES

The possibility to modify the molecule of Azelaic acid and increase the moisturizing and anti-inflammatory properties can be regarded has an important breakthrough in the development of the molecule. Indeed, new application fields can be identified in the light of new therapeutic uses of azelaic acid such as **in rosacea**.

Interest for
DERMATOLOGISTS

AZELOGLICINA®

Recently, azelaic acid, after being utilized for years **in acne**, has been proven to be highly efficacious at 20 % in the treatment of **rosacea** becoming in few months the leading product in the US market.

AZELOGLICINA®, a combination between azelaic acid and glycine, can be a further development in the cosmetic management of this condition. Indeed, this molecule is generally more safe and well tolerated compared to azelaic acid itself, while keeping the same beneficial activity of the original molecule; furthermore, its binding to 2 moles of glycine can characterize it with more pronounced moisturizing properties as well as an increased stability and compatibility in cosmetic formulations. Recent studies have shown the efficacy of **AZELOGLICINA®** as a **skin lightening** and **sebum normalizer** agent associated with **moisturizing capabilities** opening new interesting approaches to the cosmetic treatment of **hyperpigmented disorders**.

In conclusion, **AZELOGLICINA®** can be regarded as a functional cosmetic ingredient which can successfully be used in formulations used for the management of seborrhea, rosacea and hyperpigmented disorders.

FORMULATIONS

AZELOGLICINA®

1 Hydroalcoholic lotion for impure skin

AQUA	q.b. 100
GRAMBEN II *PROPYLENE GLYCOL, DIAZOLIDINYL UREA, METHYLPARABEN, PROPYL PARABEN*	1,00%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
BISABOLOL	0,40%
SALICILIC ACID	0,50%
ALCOHOL	15,00%

pH: 6.50 - Clear Solution

2 Gel for oily and impure skin

AQUA	q.b. 100
GRAMBEN II *PROPYLENE GLYCOL, DIAZOLIDINYL UREA, METHYLPARABEN, PROPYL PARABEN*	1,00%
HYDROXYPROPYL GUAR	1,20%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
TIOLISINA COMPLEX 30 *LYSINE CARBOXYMETHYL CYSTEINATE, LYSINE THIAZOLIDINE CARBOXYLATE*	2,50%
BISABOLOL	0,40%
PEG-40 HYDROGENATED CASTOR OIL	2,00%

pH: 6.80 - viscosity: 1.500 mPa.s

3 Non ionic O/W emulsion

AQUA	q.b. 100
CETEARYL GLUCOSIDE, CETEARYL ALCOHOL	5,00%
GLYCERYL MONOSTEARATE	1,20%
BISABOLOL	0,80%
SQUALANE	8,00%
OLEA EUROPAEA OIL	2,00%
RETINYL ACETATE	0,20%
ZINCUM GLUCONATE	1,00%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
XANTHAN GUM	0,30%
FENOSSIPARABEN MPJ *PHENOXYETHANOL, METHYLPARABEN, ETHYLPARABEN, GLYCERIN*	0,50%
RED ALGA GEL *ALGAE EXTRACT*	5,00%

pH: 6.00 - viscosity: 5.000 mPa.s

4 Anionic Emulsion

PHYTOCREAM 2000 *POTASSIUM PALMITOYL HYDROLIZED WHEAT PROTEIN, GLYCERYL STEARATE, CETARYL ALCOHOL*	10,00%
GLYCERYL MONOSTEARATE	1,80%
BISABOLOL	0,80%
SQUALANE	8,00%
OLEA EUROPAEA OIL	2,00%
RETINYL ACETATE	0,20%
ZINCUM GLUCONATE	1,00%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
XANTHAN GUM	0,30%
FENOSSIPARABEN MPJ *PHENOXYETHANOL, METHYLPARABEN, ETHYLPARABEN, GLYCERIN*	0,50%
RED ALGA GEL *ALGAE EXTRACT*	5,00%

pH: 6.50 - Clear Solution

5 O/W emulsion with zinc oxide

AQUA	q.b. 100
CETEARYL GLUCOSIDE, CETEARYL ALCOHOL	5,00%
GLYCERYL MONOSTEARATE	1,20%
BISABOLOL	0,80%
ETHYLHEXYL ISONONANOATE	8,00%
C 15-20 ALKYL BENZOATE	2,00%
ZINC OXIDE	10,00%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
SF 18-350 *DIMETHICONE*	0,45%
FENOSSIPARABEN *PHENOXYETHANOL, METHYLPARABEN, ETHYLPARABEN, PROPYLPARABEN, BUTYLPARABEN*	1,00%
PANTENOL, GLYCERIN	5,00%
CARBOMER	0,20%
XANTHAN GUM	0,20%
AMINOMETHYLPROPANOL	q.b.

pH: 6.80 - viscosity: 1.500 mPa.s

6 Hyperfluid nanoemulsion

AQUA	q.b. 100
NANOCREAM *POTASSIUM PALMITOYL OAT AMINOACIDS, PALM GLYCERIDES, CAPRILOYL GLYCINE*	10,00%
LECITHIN	1,00%
BISABOLOL	0,80%
ETHYLHEXYL ISONONANOATE	4,00%
DICAPRYLYL ETHER	4,00%
AZELOGLICINA ***POTASSIUM AZELOYL DIGLYCINATE***	5,00%
FENOSSIPARABEN MPJ *PHENOXYETHANOL, METHYLPARABEN, ETHYLPARABEN, GLYCERIN*	1,00%
PANTENOL, GLYCERIN	1,00%

pH: 6.00 - viscosity: 5.000 mPa.s

Toxicological *data*

AZELOGLICINA® INCI Name: Potassium Azeloyl Diglycinate after following toxicological tests:

Test/Study	**Toxicological endpoint**
Eye Irritation in vitro (Irritection test)	Not irritant
Dermal irritation (irritection test)	Not irritant
Eye Irritation in vitro (HET-CAM)	Not irritant
Skin Irritation (patch test)	Not irritant
Hypoallergenicity	Not allergenic
Oral toxicity	$LD_{50} \geq 2000$ mg/Kg
Skin sensitisation (RIPT Testing)	Not sensitizing
Phototoxicity UV (in vitro)	Complies

could be generally recognized as safe for cosmetic use

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