GLISTIN®

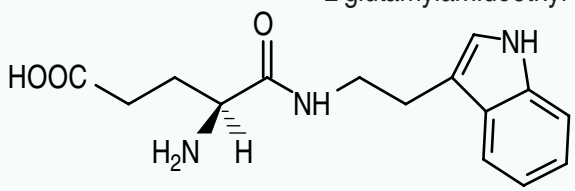
EXSYMOL

Aqueous solution of L-glutamylamidoethyl indole
INCI Denomination : GLUTAMYLAMIDOETHYL INDOLE (and) WATER

Origin

GLISTIN® is a stable aqueous solution of the synthetic dipeptide L-glutamylamidoethyl indole.

L-glutamylamidoethyl indole



Composition

L-glutamylamidoethyl indole	1.00 %
Sodium methyl paraben	0.14 %
Water sq	100.00 %

Technical Characteristics

limpid, colorless liquid
pH: around 7.0
Density at 20°C: around 1.0
Miscible with water, alcohols and glycols

Availability

1, 5 or 30 kg drums

Uses

cosmetic neuroprotection

*

anti neuronal degenerescence, neurotrophic effect (NGF-like)

*

cutaneous neuroprotection (anti-apoptotic effect)

*

neuro-cutaneous messenger

*

anti-stress (cutaneous sensitivity)

*

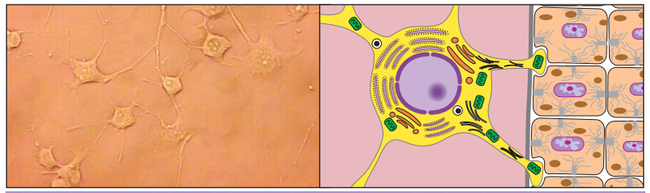
anti-aging

GLISTIN® : CUTANEOUS NEUROACTIVE

The nervous system controls the skin with its terminal ramifications...

It is more and more commonly accepted that the nervous system is involved in the cutaneous anatomy and physiology. The cosmetic industry, mainly involved in improving someone's look, has gone beyond its limits and has had to develop new activities or even sensations. In that context, the cosmetic experts interested in the nervous system developed **GLISTIN®**.

It has effectively been demonstrated and observed by electronic microscopy, that some relations exist between the nervous fibres and some cutaneous cells such as keratinocytes, melanocytes, immune cells, fibroblasts, adipocytes... Moreover, the cutaneous cells have the properties of not only producing neuromediators but also of being the target when possessing some receptors. For example, keratinocytes synthesize cutaneous neuromediators and have as well some receptors for the substance P, which is a neuropeptide.



Skin's good health and care are linked with a good protection of the cutaneous nervous system

Because of the important role of the cutaneous nervous system, the cosmetic experts are concerned about its protection and stimulation. The objective is to mainly protect its optimum skills and therefore to maintain an excellent cutaneous quality on a metabolic and immune basis.

Unlike other cutaneous cells, the nervous ones have a very low power of regeneration (or renewal). Therefore, the aim is to **maintain their functional reactive capacities** and to **protect them from aggressions**. The neurotrophic factors such as NGF (Nerve Growth Factor) have such properties to fill in this function.

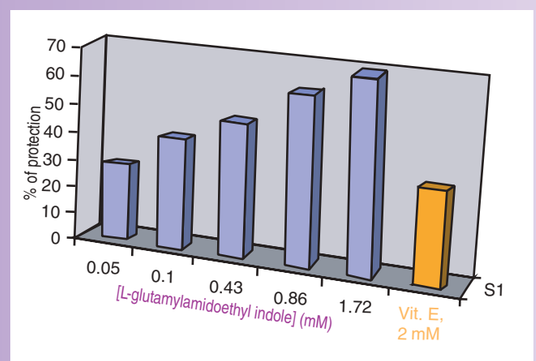
The tests done with **GLISTIN®** have shown that such neutrophic and anti-neuronal degenerescence activities could be evidenced.

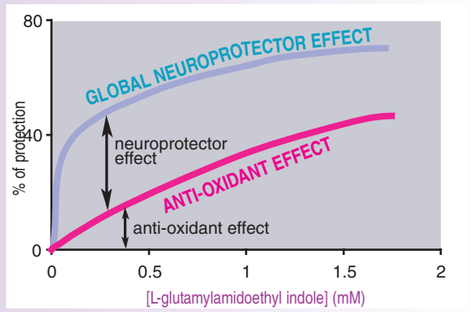
Neuroprotection

Neuroprotection is more than just an «ordinary» anti-oxidant activity

The PC12 cells, which are nervous cells, are not renewed ; therefore they have to be carefully protected against damages, such as UV oxidation, which could prematurely kill them.

The neuroprotector effect of L-glutamylamidoethyl indole, much more efficient than the one of vitamine E, has been evidenced, after UVB irradiation of nervous cells at 285 nm.



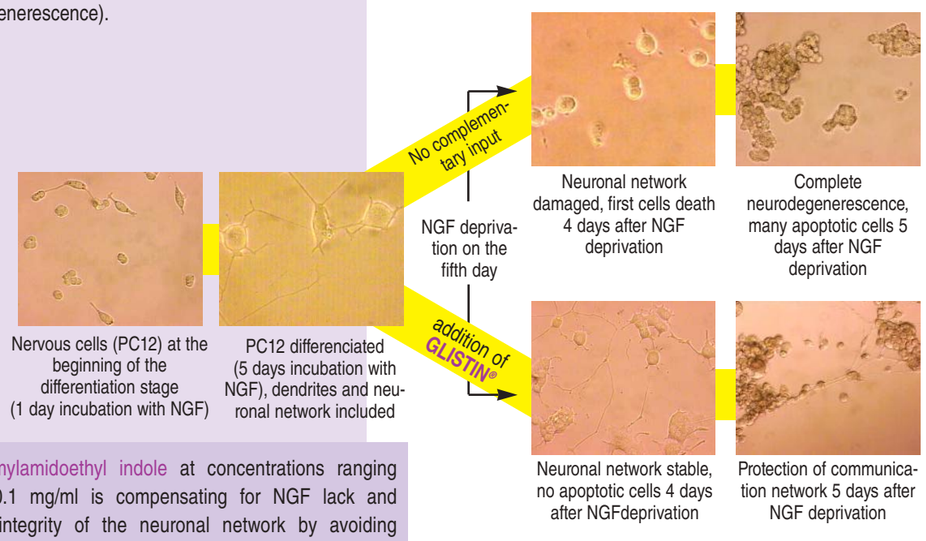


The anti-oxidant effect of **GLISTIN®** was observed on the «model system», which included hypoxanthine and xanthine-oxydase as oxidation generator of a standard molecule (deoxyribose). It has been shown that this anti-oxidant effect was not representing 100 % of the protection specially at low concentrations. Indeed, at concentrations lower than 0.25 mM, the anti-oxidant effect does not exceed 10 % whereas 0.1 mM of L-glutamylamidoethyl indole is inducing already a very good protection of PC12 cells. This clearly reveals that one important aspect of the neuroprotection depends on a different effect than the anti-oxidation. **This predominant effect is defined as neurotrophic, able to develop the functions of neurospecific factors such as, for example, NGF (Nerve Growth factor)**.

Neurotrophic effect

The growth of the nervous cells is widely different from the other types of cellls since they are not renewed. Therefore any damage will have a crucial impact on them compared to the other ones. Moreover, the apoptotic process, the «positive» programmed death for the seriously damaged cells, is the ultimate step for the nervous cells.

Their growth has to go through a differentiation stage. The undifferentiated precursor cells (morphologically non distinct), will be transformed into nervous cells, morphologically characterized by the presence of dendrites. The differentiation process occurs with the help of neurotrophic factors such as NGF. It is clearly observed that nervous cells (PC12) in an enriched NGF culture lead to an optimum differentiation characterized by the presence of dendrites as well as of an important neuronal netwok. On the opposite, a lack of NGFwill end up in a damaged network and into the cells' apoptotic death (neurodegenerescence).



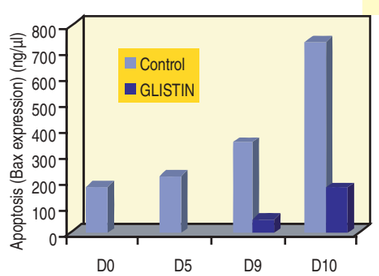
Adding L-glutamylamidoethyl indole at concentrations ranging from 0.05 to 0.1 mg/ml is compensating for NGF lack and maintains the integrity of the neuronal network by avoiding the neurodegenerescence as well as the apoptotic death of the nervous cells.

Anti-apoptotic effect

Unlike most cells, the programmed nervous cells' death (apoptosis) is «an end in itself» since those specific cells are not renewed. One direct consequence of the neurotrophic effect, already tested, is a decrease of apoptotic cells.

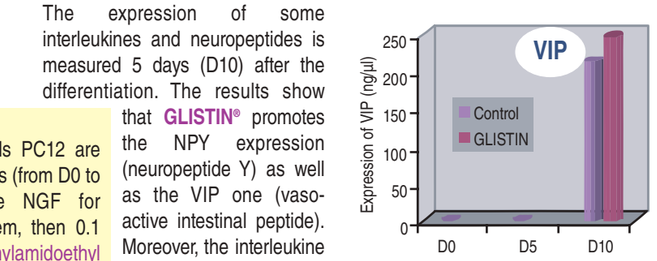
This phenomenon qualitatively observed on the above photos, was also confirmed by a quantitative test on the PC12 cells, by measuring an pro-apoptotic inhibitor (Bax) using RT-PCR.

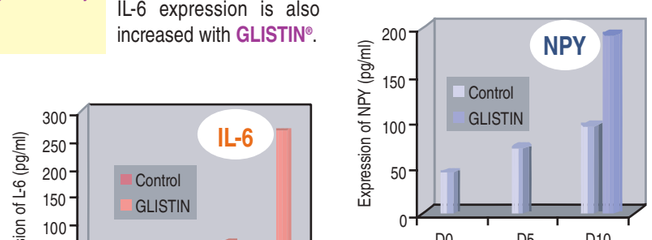
The nervous cells PC12 are cultured for 5 days (from D0 to D5) with some NGF for differentiating them, then 0.1 mg/ml of L-glutamylamidoethyl indole is added.



Proposal of a mechanism : expression of interleukines and neuropeptides...

The expression of some interleukines and neuropeptides is measured 5 days (D10) after the differentiation. The results show that **GLISTIN®** promotes the NPY expression (neuropeptide Y) as well as the VIP one (vaso-active intestinal peptide). Moreover, the interleukine IL-6 expression is also increased with **GLISTIN®**.





Tolerance Study

Clinical tests have been peformed to evidence the safety of GLISTIN® for cutaneous irritability, sensitization, phototoxicity and photoallergy.
The tolerance of GLISTIN® has also been studied *in vitro* by non animal alternative methods. The ocular tolerance is evaluated by studying the cytotoxicity on fibroblast culture isolated from rabbit cornea and also by Het Cam techniques. The cutaneous tolerance is evaluated on human skin explants. The results observed show that :

- GLISTIN® is not irritant.

The potential mutagenic activity of GLISTIN® has also been studied by Ames tests. No mutagenic activity was induced on the selected bacterial strains.

Formulation

Avoid light-exposure and use opaque packaging. The incorporation of anti-oxidant and metals scavengers would increase the stability of it. GLISTIN® is not sensitive to temperature.
The recommended concentration is about 1%.

Existing Studies

Investigation of the protective activity of an active ingredient against cutaneous neuronal degenerescence *(SCC Technology Showcase, New-York, Dec. 2002)*

*

Protection of cutaneous neurons by a new peptidomimetic endowed with neurotrophic and anti-apoptotic properties *(IFSCC Congress, Seoul, Sep. 2003)*

*

Study of the neuroprotective and anti-apoptotic properties of ETRY50, a new neurotrophic agent *(IID Congress, Miami, May 2003)*

*

Toxicity - Tolerance

EXSYMOL S.A.M. - 4 avenue du Prince Héréditaire Albert - MC 98000 MONACO
Tel. : +377 92 05 66 77 - Fax : +377 92 05 25 02
E-mail : exsymol@exsymol.com - Internet : http://www.exsymol.com