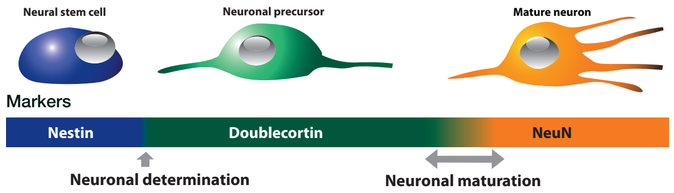
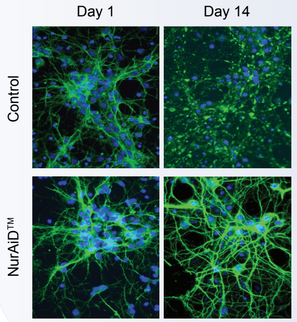
NurAiD™ amplifies endogenous processes of neuronal self-repair and self-defense throughout the neuronal life cycle



NurAiD™ increases self-repair mechanisms in the brain



1. NurAiD™ promotes a denser network of connections and the formation of synapses

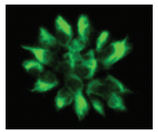
On day 14, in neuronal cell cultures treated with NurAiD™, epifluorescence showed a remarkable increase of DCX, GAP43 and Synaptotagmin expressions, providing evidence that NurAiD™ triggers:

- **Neurogenesis**
- **Neurite outgrowth**
- **Synaptogenesis**

DCX is a microtubule-associated protein specifically expressed in neuronal precursors and in areas of continuous neurogenesis in the adult brain. GAP43 is a growth associated protein determinant in the regulation of neurite outgrowth, growth cone guidance and synaptic plasticity. Synaptotagmin is a synaptic protein involved in synaptogenesis and synapse function.

2. NurAiD™ stimulates the proliferation of human stem cells

NurAiD™ promotes neurogenesis which corresponds to the production of new born neurons in human stem cell models. After 2 days of treatment, low density cultures treated with NurAiD™ showed a 3-fold increase of radiating clusters in Nestin-positive progenitors (p<0.01).



Nestin is an intermediate filament protein that is implicated in axon growth.

3. NurAiD™ enables neuronal cells to integrate into mature neuronal networks

NurAiD™ results in 2.1-fold increase in the number of mature migrated neurons (p<0.01).

Heurteaux, Neuropharmacology, 2010

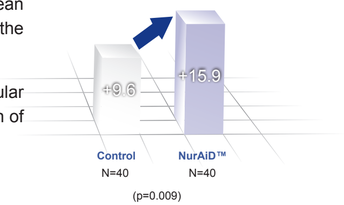
4. By stimulating microcirculation, NurAiD™ presents an interesting strategy to enhance neuroplasticity

The treatment group (N=40) recorded significantly higher score at 3 months on Barthel Index and a higher mean change in Cerebral Blood Flow Velocity compared to the placebo group.

These 2 effects point towards a change in the vascular resistance of microcirculation vessels and the promotion of angiogenetic activity, hence playing a role in:

- Generation of new neurons
- Rewiring processes of neuroplasticity
- Preventing neuronal death in penumbra at the acute stage of brain infarction

Change in Mean Flow Velocity between Baseline and Month 3 (cm/s)



European Journal of Internal Medicine, 2011

Increases secretion of BDNF → Increases proliferation of neuronal stem cells → Stimulates the conversion to mature neurons → Improves microcirculation → Promotes synaptogenesis and axonal and dendritic plasticity → Promotes dense network of connections and restores neuronal circuits

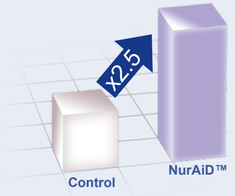
Mechanism of action

NurAiD™ increases Brain Derived Neurotrophic Factor (BDNF) production

BDNF expression level increased by 2.5-fold after 6 weeks of treatment with NurAiD™ in rodent models (p<0.01).

- BDNF is a growth factor which **activates neurogenesis**
- BDNF **improves neuronal survival**
- BDNF **favors proliferation and differentiation of new neurons**

BDNF level more than doubled after 6 weeks of treatment



NurAiD™ triggers the activation of AKT pathway

NurAiD™ increases the Protein Kinase B (AKT) level by 2.25-fold compared with vehicle treated group. This represents an important observation for stroke management.

NurAiD™ amplifies a number of self-defense processes in the brain

- NurAiD™ **decreases DNA fragmentation caused by ischemia** (Apoptotic signaling cascade)
- NurAiD™ **decreases the number of cells undergoing apoptotic cell death**
- NurAiD™ **decreases cell suffering** (Excitotoxicity phase), **increases neuronal survival** and **reduces infarct volume**
- NurAiD™ **drastically decreases lipid peroxidation produced by free radicals** which reduces infarct volume
- NurAiD™ **is an apoptosis inhibitor**. It inhibits both the apoptotic cascade and fragmentation of DNA as well as promotes neuronal survival by decreasing Bax expression and activating the AKT pathway

Activates the AKT pathway → Inhibits apoptotic cascade & reduces free radicals → Decreases cell suffering after glutamate aggression → Decreases DNA fragmentation → Increases survival rate and reduces infarct volume in ischemic penumbra → Protects fragile zones of the hippocampus responsible for memory

Recovery of neurological functions resulting in better functional activities

Recovery of neurological functions already observed in humans, both in clinical trials and clinical practice, can be quantified in well established animal models.

- **Cognitive impairments**

  NurAiD™ improved spatial navigation and memory skills by considerably **shortening escape latencies** in treated rodents compared to vehicle (p<0.05) in global ischemic models.

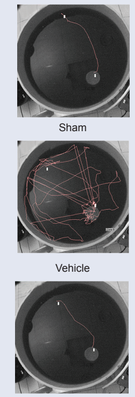
- **Locomotor deficits**

  NurAiD™ significantly increased by **150%** locomotor performances of treated rodents compared to vehicle group at Day 3 (p<0.001) after global ischemia.

- **Strength deficits**

  Grip strength test showed that NurAiD™ significantly improved muscle strength force of treated rodents compared to vehicle group in a global ischemia model. The treated groups progressively returned to the strength force of pre-surgery and sham-operated levels at 10 days after reperfusion, while vehicle group showed a significant decrease (p<0.001).

Morris water maze



In Morris maze test, the swim pattern of sham-operated group and treated group revealed the direct route to the pedestal while vehicle treated were engaged in a complex search pattern.

Quintard, Neuropharmacology, 2011

Key facts to remember about NurAiD™

Pharmacology

- ✓ Amplifies self-defense and self-repair processes of the brain
- ✓ Stimulates production of the growth factor BDNF
- ✓ Promotes neurogenesis and maturation of new born neurons
- ✓ Increases neurite outgrowth and synaptogenesis
- ✓ Improves microcirculation and increases Cerebral Blood Flow velocity
- ✓ Prevents lipid peroxidation due to free radicals

Efficacy

- ✓ 2.4 greater chance of achieving independence
- ✓ 70% reduction of motor deficits at 3 months
- ✓ After 3 months, treatment can result in significant improvements in motor, speech, visual and cognitive functions
- ✓ Provides a better recovery of neurological functions post-stroke

Safety

- ✓ Proven safe as an add-on treatment at acute and chronic stages of stroke recovery
- ✓ No interaction with aspirin

Prescription

- ✓ NurAiD™ should be initiated as soon as possible after stroke onset, and up to 6 months post-stroke
- ✓ Routinely prescribed for **ischemic, hemorrhagic** strokes and **TBI** patients
- ✓ Take 2 capsules, 3 times a day, for 3 months

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Note:
NurAiD™ is a trademark of Moleac. MLC601 and MLC901 are 2 different proprietary formulae which have been shown to be equivalent in pharmacology and are referred as NurAiD™ in the brochure.

Abbreviated Prescribing Information

NurAiD™ II (MLC 901) Capsules 400mg

INDICATION
Post-stroke recovery.

DOSAGE AND METHOD OF ADMINISTRATION
Dosage: Take 2 capsules, 3 times a day, for 3 months.

METHOD AND ROUTE OF ADMINISTRATION
Oral administration. The capsules must be taken as a whole. Content can also be diluted in water, to be drunk or administered via gastric tube.

CONTRAINDICATION
The use of NurAiD™ in children or pregnant and lactating women is not well-established. No contraindication is known to date.

MONITORING
To date, no harmful interactions between NurAiD™ and other drugs have been reported.

As a routine precaution, patients on oral anti-coagulants are advised to have their INR initially monitored in a way similar to any changes in their prescription.

STORAGE CONDITIONS
To be kept sealed and stored in a cool and dry place. Keep away from children.

PRESENTATION
Each pack contains three boxes each with five blisters of 12 capsules, corresponding to a 30-day treatment.

Full Prescribing Information available on request from Moleac.

Moleac

More information at www.moleac.net
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Fax: +33 148784831

NurAiD™ II has an improved dosage form and a convenient 30-day treatment pack!

NurAiD™ II MLC 901

Pharmacology of NurAiD

NurAiD™ amplifies endogenous processes of Neuronal Self-Repair and Self-Defense mechanisms in the brain

Moleac