

SUMMARY OF PRODUCT FEATURES

Product Name:	NEURALCIM® (Recombinant human erythropoietin low sialic acid)
Dosage form:	Nasal Instillation Solution
Fortaleza:	1 mg/mL
Presentation:	Case with 1 case per 6 1 mL colorless glass bulbs, 6 sterile 1 mL plastic disposable syringes with needle, and 2 dose limiters
Holder of the Health Registry, city, country:	CENTER FOR MOLECULAR IMMUNOLOGY, Havana, Cuba
Product manufacturer(s), city(s), country(s):	1. Recombinant Protein and Therapeutic Vaccines Production Plant (Plant 1). Active pharmaceutical ingredient. 2. Final processing plant (plant 3). Finished product. B-22-016-N07-C
Health Registration Number:	
Date of Registration:	March 1, 2022
"This authorization is based on the positive results of clinical studies of human pharmacology and therapeutic exploration of the product. It has been conditioned on the presentation of the results of the therapeutic confirmation studies. Its administration must be supervised by a specialist doctor with experience in the treatment of Mild and Moderate Alzheimer's Disease."	
Composition:	
<i>(Active Pharmaceutical Ingredient, quantity and quality reference)</i>	
Each 1 mL bulb contains:	
Recombinant human erythropoietin low sialic acid	1 mg
Sodium chloride	
Hydroxypropyl methylcellulose	
K4M Monobasic Sodium	
Phosphate Dibasic Sodium	
Phosphate Polysorbate 80	
Disodium Ethylenediaminetetraacetic Acid (EDTA)	
Water for Injection	
Validity period:	12 months
Storage conditions:	Store at 2°C and 8°C. Do not freeze. Protect from light.

Therapeutic indications:

Mild and Moderate Alzheimer's Disease.

Contraindications:

Patients who have a history of hypersensitivity to compounds of similar chemical or biological composition to the components of the formulation of this product.

Precautions:

The administration of any biological product should be careful and due precautions should be taken in case of allergy or unexpected reaction.

It must be ensured that the airways are permeable.

Special warnings and precautions for use:

NEURALCIM® must be prescribed by a doctor.

NEURALCIM® does not contain any preservatives in the formulation, for this reason, it should be used immediately after opening the bulb. Medical supervision is indicated in patients with chronic rhinitis.

Keep out of reach of children

Undesirable effects:

Most adverse events that occur with the use of NEURALCIM® are mild in intensity, reversible, and do not result in treatment changes. There have been no serious adverse reactions related to the drug.

The most frequent adverse reactions (5-10%) presented during the course of the clinical development program in patients with neurological conditions were: high blood pressure, nasopharyngeal burning, nausea, increased hepatic enzyme alanine aminotransferase (ALAT), headache, sneezing, and burning of the nasal mucosa.

The phase II-III, multicenter, parallel, controlled, adaptive, randomized, and double-blind clinical trial in patients with a confirmed diagnosis of Alzheimer's disease included 174 patients. Only 22 adverse events were reported, with a very low frequency of occurrence. The most frequent were: vomiting (3; 13.6%), headache and bronchopneumonia with 2 (9.09%) each, these not related to the product. The rest of the adverse events had a frequency of less than 1%. Most of them were: non-serious 16 (72.7%), mild intensity 11 (50.5%), no changes in the administration of the product 17 (77.3%), reversible 18 (81.8%) and unrelated to the treatment under study 21 (95.5%). No serious event related to the use of NEURALCIM® was reported. The only adverse event possibly related to the investigational product was numbness of the right upper limb.

Dosage and mode of administration:

Treatment with NEURALCIM® for Alzheimer's disease should be administered 1 time a day, 3 times a week, on alternate days.

Each dose of 0.5mg/mL is instilled nasally, subdivided into doses of 0.25 mL in each nostril.

How to prepare.

1. Check the shelf life declared on the label and that the product has been stored at a temperature of 2 to 8°C.

2. Before administering the product, steep it for 10 minutes at room temperature.
3. Prior to application, shake the bottle (bulb) gently.

How to administer:

1. Explain to the patient the procedure to be performed and ask for their cooperation.
2. Have your child gently wipe his or her nose to remove any remaining discharge.
3. Lay the patient supine (face up figure 1). Place a pillow under the shoulders (scapular region), so that the head remains tilted dorsally at 45 degrees from the body's axis. Maintain this position throughout the application, which ensures that the drops reach the necessary place.
4. Load the supplied 1 mL syringe with the product to the value of 0.5 mL and remove the needle from the syringe.
5. Insert the dose-limiting device as directed in Figure 2
6. Pick up the syringe with your predominant hand. With the index finger of your other hand, press into the nostril on the side away from where you are going to apply the medicine.
7. Insert the tip of the syringe (without a needle) into the nostril as deeply as possible without harming the patient (Figure 3) and apply the indicated amount (0.25 mL) of the medication drop by drop slowly, until you reach the top of the limiting device.
8. Remove the limiting device and insert the syringe into the other nostril and proceed in the same way as in point 10.
9. Keep the patient in the same position for at least 5 minutes.
10. It does not require hospitalization, it can be applied on an outpatient basis, under prescription and monitoring by a doctor.

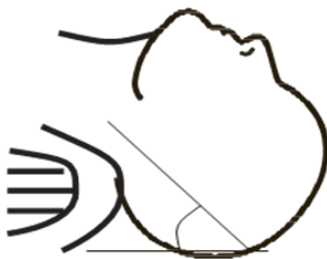


Figure. 1.

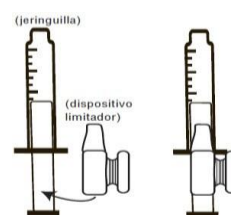


Figure. 2



Figure. 3.

Interactions with other medicinal products and other forms of interaction:

The concomitant use of zinc sulfate and NEURALCIM® inhibits the therapeutic effect.

In the clinical trial in patients with mild/moderate Alzheimer's disease, no drug interactions were observed between the drugs administered (vitamins, antihypertensives, diuretics, tricyclic antidepressants, and hypoglycemic agents) and the investigational product.

Use in pregnancy and lactation:

There are no data on the use of NEURALCIM® in pregnant women in clinical trials, but the proteins are known to cross the placental barrier. Therefore, as a preventive measure, the use of NEURALCIM® in pregnant women is not recommended unless the expected benefit outweighs the potential risk.

The length of time NEURALCIM® stays in the body is unknown. It is not known whether NEURALCIM® is excreted in breast milk, so women should not breastfeed their children during treatment with NEURALCIM®. No data are available regarding the effects of NEURALCIM® on fertility.

Effects on the driving of vehicles and machinery:

The effects of NEURALCIM® on vehicle/machine driving are unknown. The influence of NEURALCIM® on the ability to drive and use machines is expected to be minimal.

However, if after the onset the individual develops dizziness, confusion, drowsiness or fatigue, he should be warned to avoid driving vehicles or using machines.

Overdose:

The effects of overdosing with NEURALCIM®.

Pharmacodynamic properties:

ATC Code: N07XX

Pharmacotherapeutic Group: N- nervous system, N07- other drugs for the nervous system, N07X- other drugs for the nervous system, N07XX- other drugs for the nervous system

NEURALCIM® performs its pharmacological function as a neuroprotective agent. It acts in the brain in a paracrine/autocrine way, activating multiple signaling mechanisms to inhibit apoptosis and therefore inhibits neuronal cell death; it reduces inflammation and local edema; it induces overexpression of the EPO receptor; it increases the levels of Brain-Derived Neurotrophic Factor (BDNF) and the enzyme Glutathione-S-transferase (GST), the main defense against xenobiotics of exogenous or endogenous origin, in cortical and subcortical regions; it induces the synthesis of the Neuroglobin protein selectively in damaged regions; it induces angiogenesis and prolongation of capillaries; it protects the vascular endothelium. It contributes directly to neurogenesis and finally to neuroplasticity that guarantees new homeostasis and rescue of damaged or lost functions due to injury to the brain.

The pharmacodynamic properties (neuroprotective mechanism) have been evaluated in animal models of neurodegenerative diseases. In induced murine and double transgenic models of Alzheimer's disease, NEURALCIM® showed a decrease in neuroinflammation, oxidative stress, cellular apoptosis, prevented behavioral alterations in the cognitive area of Alzheimer's disease pathology and decreased plaque-associated amyloid beta. In other animal models with neurological alterations (SCA2 ataxia and cerebral ischemia), the use of NEURALCIM® has caused a delay in the onset of ataxic symptoms, a decrease in brain tissue damage and the area and volume of cerebral infarction. Motor and sensory function has also improved, with a decrease in associated mortality.

The results obtained in the phase II-III clinical study, in patients with a confirmed diagnosis of Alzheimer's disease, were positive. NEURALCIM®, stabilized the disease in most of the treated patients, achieving a high percentage of improvement in the cognitive sphere.

Pharmacokinetic properties:

NEURALCIM® is a recombinant erythropoietin with a low sialic acid content, so it degrades in the liver when administered systemically. To guarantee the therapeutic effect of NEURALCIM®, the intranasal route was selected, which is a non-invasive method of rapid release to the brain; which bypasses hepatic metabolism, involves extracellular and intracellular pathways.

Several animal studies have provided important evidence on the ability of NEURALCIM® administered intranasally to cross the nasal mucosa and reach the central nervous system, thus guaranteeing sufficient levels to exert its pharmacological effect. The administration of NEURALCIM® nasally in gerbils confirmed the passage of the molecule to the CNS, detecting its presence in olfactory bulbs and in the cerebellum. In *Macaca fascicularis*, a significant increase in EPO concentrations in CSF was observed minutes after administration.

The determination of the concentration of EPO in CSF, from a representative sample of patients with cerebellar ataxia type-2 (ACS-2) treated with NEURALCIM®, also demonstrated the increase in the median concentration.

Instructions for use, handling and destruction of the unusable remainder of the product:

Soil for nasal use.

NEURALCIM® should be visually inspected prior to use, to distinguish the presence of foreign particles or change in coloration, in which case the solution should not be used.

Verify that the bulbs are within the shelf life declared on the label and that the product has been stored at a temperature of 2 to 8 °C. Consult package leaflet.

Discard the leftover.

Date of approval / revision of the text: 2022-03-15

SUMMARY OF PRODUCT CHARACTERISTICS

Product name:	NEURALCIM® (Low sialic acid recombinant human erythropoietin)
Dosage form:	Nasal instillation solution
Strength:	1 mg/mL
Package presentation:	Carton containing 1 pack with 6 colorless glass ampoules of 1 mL, 6 sterile disposable 1 mL plastic syringes with needle, and 2 dose limiters
Marketing authorization holder, city, country:	CENTER FOR MOLECULAR IMMUNOLOGY, Havana, Cuba
Product manufacturer(s), city(ies), country(ies):	1. Recombinant Protein and Therapeutic Vaccine Production Plant (Plant 1). Active pharmaceutical ingredient. 2. Final processing plant (Plant 3). Finished product.
Health Registration No.:	B-22-016-N07-C
Registration Date:	March 1, 2022
“This authorization is based on positive results from the product’s clinical studies in human pharmacology and therapeutic exploration. It is conditional upon submission of results from therapeutic confirmation studies. Administration must be supervised by a specialist physician with experience treating mild to moderate Alzheimer’s disease”.	
Composition:	
<i>(Active Pharmaceutical Ingredient, amount, and quality standard reference)</i>	
Each 1 mL ampoule contains:	
Low-sialic acid recombinant human erythropoietin	1 mg
Sodium chloride	
Hydroxypropyl methylcellulose K4M	
Monobasic sodium phosphate	
Dibasic sodium phosphate	
Polysorbate 80	
Disodium ethylenediaminetetraacetic acid (EDTA)	
Water for injection	
Shelf life:	12 months
Storage conditions:	Store between 2°C and 8°C. Do not freeze. Protect from light.

Therapeutic indications:

Mild to moderate Alzheimer's disease.

Contraindications:

Patients with a history of hypersensitivity to compounds with a chemical or biological composition similar to the components of this product's formulation.

Precautions:

Any biological product should be administered with care, and appropriate precautions should be taken in the event of an allergy or an unexpected reaction.

Ensure that the airways remain open.

Special warnings and precautions for use:

NEURALCIM® must be used only with a doctor's prescription.

NEURALCIM® contains no preservatives in its formulation; therefore, it should be used immediately after opening the ampoule. Medical supervision is recommended for patients with chronic rhinitis.

Keep out of reach of children"

Undesirable effects:

Most adverse events reported with NEURALCIM® are mild, reversible, and do not require changes to treatment. No serious drug-related adverse reactions have been reported.

The most common adverse reactions (5–10%) reported during the clinical development program in patients with neurological conditions were: high blood pressure, nasopharyngeal irritation, nausea, increased liver enzyme alanine aminotransferase (ALT), headache, sneezing, and burning of the nasal mucosa.

The phase II–III clinical trial—multicenter, parallel-group, controlled, adaptive, randomized, and double-blind—in patients with a confirmed diagnosis of Alzheimer's disease, included 174 patients. Only 22 adverse events were reported, with a very low rate of occurrence. The most common were: vomiting (3; 13.6%), headache and bronchopneumonia with 2 (9.09%) each; these were not related to the product. All other adverse events occurred at a frequency below 1%. Most events were: non-serious 16 (72.7%), mild in intensity 11 (50.5%), with no change in product administration 17 (77.3%), reversible 18 (81.8%%), and not related to the study treatment 21 (95.5%). No serious event related to the use of NEURALCIM® was reported. The only adverse event possibly related to the investigational product was numbness of the right upper limb.

Dosage and administration:

Treatment with NEURALCIM® for Alzheimer's disease should be administered once daily, three times per week, on alternating days.

Each 0.5 mg/mL dose is administered intranasally, divided into 0.25 mL in each nostril.

Preparation instructions.

1. Check the expiration period stated on the label and confirm the product has been stored at 2 to 8°C.

2. Before administering the product, let it sit at room temperature for 10 minutes.
3. Before use, gently shake the bottle (bulb).

Directions for use:

1. Explain the procedure to the patient and ask for their cooperation.
2. Have the patient gently blow their nose to clear any remaining secretions.
3. Place the patient in the supine position (lying on their back; Figure 1). Put a pillow under the shoulders (scapular area) so the head stays tilted back at a 45-degree angle relative to the body. Keep this position throughout administration to ensure the drops reach the intended area.
4. Fill the supplied 1 mL syringe with the product up to the 0.5 mL mark, then remove the needle from the syringe.
5. Attach the dose-limiting device as shown in Figure 2.
6. Hold the syringe in your dominant hand. With the index finger of your other hand, press the nostril on the opposite side from where the medication will be applied.
7. Insert the tip of the syringe (without the needle) into the nostril as deeply as possible without injuring the patient (Figure 3) and slowly apply the indicated dose (0.25 mL) drop by drop until you reach the stop on the dose-limiting device.
8. Remove the dose-limiting device, insert the syringe into the other nostril, and proceed the same way as in step 10.
9. Keep the patient in the same position for at least 5 minutes.
10. Hospitalization is not required; it may be administered on an outpatient basis with a physician's prescription and follow-up.

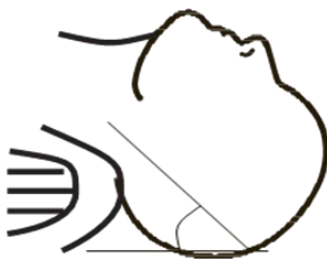


Figure 1.

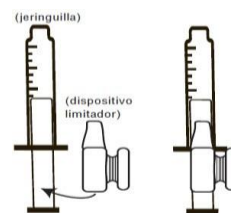


Figure 2



Figure 3.

Interactions with other medicinal products and other forms of interaction:

Using zinc sulfate together with NEURALCIM® reduces its therapeutic effect.

In the clinical trial involving patients with mild to moderate Alzheimer's disease, no drug interactions were observed between the medications given (vitamins, antihypertensives, diuretics, tricyclic antidepressants, and hypoglycemic agents) and the investigational product.

Use during pregnancy and breastfeeding:

There are no clinical-trial data on the use of NEURALCIM® in pregnant women; however, proteins are known to cross the placental barrier. Therefore, as a precaution, NEURALCIM® is not recommended during pregnancy unless the expected benefit outweighs the potential risk.

How long NEURALCIM® remains in the body is unknown. It is also unknown whether NEURALCIM® is excreted in breast milk; therefore, women should not breastfeed while receiving NEURALCIM®. No data are available regarding the effects of NEURALCIM® on fertility.

Effects on driving and operating machinery:

The effects of NEURALCIM® on driving and/or operating machinery are unknown. NEURALCIM® is expected to have minimal impact on the ability to drive or use machines.

However, if after administration the individual experiences dizziness, confusion, drowsiness, or fatigue, they should be advised to avoid driving vehicles or operating machinery.

Overdose:

The effects of an overdose of NEURALCIM® are not known.

Pharmacodynamic properties:

ATC Code: N07XX

Pharmacotherapeutic Group: N—nervous system; N07—other nervous system drugs; N07X—other nervous system drugs; N07XX—other nervous system drugs

NEURALCIM® exerts its pharmacologic action as a neuroprotective agent. It acts in the brain via paracrine/autocrine pathways, activating multiple signaling mechanisms to inhibit apoptosis and, therefore, neuronal cell death; it reduces inflammation and localized edema; it induces overexpression of the EPO receptor; it increases levels of Brain-Derived Neurotrophic Factor (BDNF) and the enzyme glutathione S-transferase (GST), a key defense against xenobiotics of exogenous or endogenous origin, in cortical and subcortical regions; it selectively induces synthesis of the protein neuroglobin in damaged areas; it promotes angiogenesis and capillary elongation; and it protects the vascular endothelium. It directly contributes to neurogenesis and, ultimately, to neuroplasticity, supporting the establishment of new homeostasis and the recovery of functions impaired or lost due to brain injury.

The pharmacodynamic properties (neuroprotective mechanism) have been evaluated in animal models of neurodegenerative diseases. In induced and double-transgenic murine models of Alzheimer's disease, NEURALCIM® reduced neuroinflammation, oxidative stress, and cellular apoptosis; prevented behavioral changes affecting cognition associated with Alzheimer's pathology; and decreased plaque-associated beta-amyloid. In other animal models with neurologic disorders (SCA2-type ataxia and cerebral ischemia), NEURALCIM® delayed the onset of ataxic symptoms, reduced brain tissue damage and the area and volume of cerebral infarction, and improved motor and sensory function, with a reduction in associated mortality.

Results from the Phase II–III clinical study in patients with a confirmed diagnosis of Alzheimer’s disease were positive. NEURALCIM® stabilized the disease in most treated patients, with a high percentage showing improvement in cognitive function.

Pharmacokinetic properties:

NEURALCIM® is a recombinant erythropoietin with low sialic acid content, so it is broken down in the liver when given systemically. To ensure NEURALCIM® delivers its therapeutic effect, the intranasal route was selected—a noninvasive method that rapidly delivers it to the brain, bypasses hepatic metabolism, and involves both extracellular and intracellular pathways.

Multiple animal studies have provided important evidence that intranasally administered NEURALCIM® can cross the nasal mucosa and reach the central nervous system, ensuring levels sufficient to produce its pharmacologic effect. Nasal administration of NEURALCIM® in gerbils confirmed the molecule’s passage into the CNS, with its presence detected in the olfactory bulbs and the cerebellum. In *Macaca fascicularis*, a significant increase in EPO concentrations in CSF was observed just minutes after administration.

Measuring EPO levels in CSF from a representative sample of patients with Spinocerebellar Ataxia type 2 (SCA-2) treated with NEURALCIM® also showed an increase in the median concentration.

Instructions for use, handling, and disposal of any unusable remaining product:

For nasal use only.

Before use, visually inspect NEURALCIM® for any foreign particles or discoloration; if either is present, do not use the solution.

Confirm the bulbs are within the expiration period stated on the label and that the product has been stored at 2 to 8 °C. See package insert.

Discard any remaining product.

Text approval / revision date: 2022-03-15