1 . TRADE NAME OF THE MEDICINAL PRODUCT

Cerebrolysin®
Solution for injection / concentrate for solution for infusion intravenous use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 215,2mg Cerebrolysin® concentrate in aqueous solution. For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type
- Post-apoplectic complications
- Craniocerebral trauma: post-operative trauma. cerebral contusion or concussion

4.2. Posology and method of administration

Single doses of up to 50 ml can be administered, but a course of therapy is the preferred option. A recommended optimum course of therapy comprises daily application over a total of 10-20 days. Daily recommendations/Daily dose:

- Organic brain disorders, metabolic disorders and neurodegenerative diseases (dementia)
  5-30 ml
- postapoplectic complications
  10-50 ml
- craniocerebral trauma
  10-50 ml
- children
  1-2 ml

The effectiveness of therapy can be increased by repeated courses, until no further benefit results. After the initial course, the frequency of doses may be reduced to 2 or 3 times per week. A treatment-free period, equal in length to the therapy course, should be allowed between successive therapy courses. Doses of up to 5 ml IM and up to 10 ml undiluted IV may be given. Doses between 10 ml up to a maximum of 50 ml are recommended only as a slow intravenous infusion after dilution with the suggested standard infusion solutions. The duration of the infusion should be between 15 and 60 mins. The compatibility over 24 hours at room temperature in the presence of light has been tested with the following standard infusion solutions:

- 0,9% sodium chloride solution (9 mg NaCl/ml)
- Ringer's solution (Na^+ 153,98mmol/l, Ca^{2+} 2,74mmol/l, K^+4,02mmol/l, Cl^- 163,48mmol/l)
- 5% Glucose

Vitamins and cardiovascular drugs may be given concomitantly with Cerebrolysin but the drugs should not be mixed with Cerebrolysin in the syringe.

4.3. Contra-indications

- Hypersensitivity to one of the components of the drug.
- Epilepsy.
- Severe renal impairment.

4.4. Special warnings and special precautions for use

Special care is indicated in cases of:

- allergic diathesis
- epileptic conditions and grand mal convulsions: Cerebrolysin treatment may result in an increase in the frequency of seizures
- although there are no data indicating that Cerebrolysin causes renal stress, the product should not be administered in the presence of existing severe renal failure

4.5. Interaction with other medicaments and other forms of interaction

On the basis of Cerebrolysin 's pharmacological profile, special attention should be given to possible additive effects when used in conjunction with anti-depressants or MAO inhibitors. In such cases, it is recommended that the dose of the anti-depressant is lowered.

Cerebrolysin should not be mixed with balanced amino acid solutions in an infusion.

4.6. Pregnancy and lactation

Animal studies did not show any indication of reproductive toxicity. However, no data are available for humans. Therefore, during pregnancy and lactation, Cerebrolysin should only be used after careful risk/benefit considerations.

4.7. Effects on the ability to drive and use machines

Clinical tests of Cerebrolysin have shown no effects on the ability to drive a car or operate machinery.

4.8. Undesirable effects Immune system disorders

Very rare (<1/10.000)

Hypersensitivity or allergic reactions such as itching skin reactions, local inflammatory reactions, headache, neck pain, limb pain, fever, low back pain, dyspnoea, chills and shock-like state.

Metabolism and nutrition disorders
Rare (> 1/10.000 - 1/1.000)
loss of appetite

Psychiatric disorders
Rare (> 1/10.000 - 1/1.000)
The desired activating effects have also been associated with agitation (aggression, confusion, insomnia).

Nervous system disorders
Rare (> 1/10.000 - 1/1.000)
If injected too quickly dizziness may result
Very rare (<1/10.000)
Single oases of grand mal attacks and convulsions have been reported after administration of
Cerebrolysin

Cardiac disorders
Very rare (<1/10.000)
If injected too quickly palpitations or arrhythmias may result.

Gastro-intestinal disorders
Very rare (<1/10.000)
Dyspepsia, diarrhoea, constipation, vomiting and nausea.

Skin and subcutaneous tissue disorder
Rare (> 1/10.000 - 1/1.000)
If injected too quickly, feelings of heat or sweating may result. Pruritus.

General disorders and administration site conditions:
Very rare (<1/10.000)
Injection site reactions, such as erythema and burning have been reported.

In a study rare cases (> 1/10.000 - 1/1.000) of hyperventilation, hypertension, hypotension, tiredness, tremor, depression, apathy, drowsiness and symptoms of influenza (e.g. cold, cough, infections of the respiratory tract) were reported.
As Cerebrolysin is used in the elderly, and the above mentioned undesirable effects are typical of this patient population, they may also be observed without drug use.

4.9. Overdose

There are no known instances of health-related negative effects due to overdose or intoxication.

5.PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Cerebrolysin stimulates cell differentiation, bolsters nerve cell function, and induces mechanisms of protection and repair. In animal experiments, Cerebrolysin directly influences neuronal and synaptic plasticity, thus improving learning. This has been shown in young, adult, and aged animals with reduced cognitive abilities. In models of cerebral ischaemia. Cerebrolysin reduced the infarct volume, inhibited oedema formation, stabilised microcirculation, doubled the survival rate, and normalised lesion-related neurological failure and learning deficits. Positive results were also obtained using models of Alzheimer's disease. In addition to its direct effects on neurons, Cerebrolysin appears to significantly increase the number of glucose transport molecules in the blood-brain barrier, thereby balancing out the critical energy deficit associated with this disease.

Quantitative EEG studies of healthy volunteers and patients suffering from vascular dementia have shown dose-dependent acute effects of elevated neuronal activity (increase in alpha and beta frequencies) after 4 weeks of treatment. Regardless of the cause of the disease, be it neurodegenerative dementia of Alzheimer's type or vascular dementia, Cerebrolysin therapy results in improvement in the objective cognitive abilities and in the activities of daily living. After only two weeks, there are improvements in the clinical global impression, which increase with continuation of the therapy. Also independent of the type of dementia, approximately 60-70 % of patients respond positively to Cerebrolysin therapy. In the case of senile dementia of Alzheimer's type, the improved clinical state of the patient is maintained after the end of active treatment. In particular, the activities of daily living are improved and stabilised over the long term, which in general leads to a reduced need for patient care and supervision. On the basis of its neurotrophic (nerve growth factor-like) activity, Cerebrolysin can achieve a significant reduction, or in some cases even the cessation of progression, of neurodegenerative processes.

5.2. Pharmacokinetic properties

The peptide fraction consists of short biological peptides similar or identical to those produced endogenously. Direct measurement of pharmacokinetic properties has not been performed successfully. Indirect pharmacokinetic data have been established on the basis of Cerebrolysin´s pharmacodynamic profile. The neurotrophic activity of Cerebrolysin can be detected in Blood plasma up to 24h after a single application.

Furthermore, components of the drug can cross tine blood-brain barrier. Preclinical in vivo experiments revealed identical pharmacodynamic actions on the central nervous system following intra-cerebroventricular or peripheral application. Thus, indirect evidence for the passage of components of the drug across the blood-brain barrier has been established.

5.3. Preclinical safety data

Acute Toxicity/LD50

Rat male 68ml/kg BW IV

Rat female 74mVkg BW IV

Dog male/female >52.2mi/kg BW IV

Chronic Toxicity

Rat: Above 5 ml/kg BW/day for 26 weeks: moderate changes in blood counts.

Dog: The highest applied dose of 9 ml/kg BW/day for 28 days (corresponding to approximately 10 times the human therapeutic dose) and the highest applied dose of 4.5 ml/kg BVV/day (corresponding to approximately 5 times the human therapeutic dose) for 26 weeks showed no substance-related systemic intolerability.

Reproductive Toxicity

Intravenous administration of Cerebrolysin at doses toxic to the mother, or of the highest possible volume, showed no evidence of teratogenetic effects in any phase of reproduction in rats or rabbits, no influence on fertility, breeding capacity, posterity, arid no embryotoxic or foetotoxic effects.

Mutagenicity

Cerebrolysin has shown no genotoxic or mutagenic potential, in vitro or in vivo.

Carcinogenicity

None of the studies of chronic toxicity or clinical experience have given any indication of carcinogenic effects.

Sensitising Potential

Larger molecular weight peptides with antigenic potential are excluded from the infusion solution during the manufacturing and quality control processes.

No influence on the immune system has been detected during testing. Tests revealed that Cerebrolysin does not result in the formation of antibodies or in cutaneous anaphylaxis. Cerebrolysin shows no histamine-stimulating potential and no hemagglutinating effects.

6.PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium hydroxide and water for injections.

6.2. Incompatibilities

Cerebrolysin is incompatible with solutions which change the pH (5.0-8.0) and with lipid-containing solutions.

6.3. Shelf life

Ampoules: 5 years

Vials: 2 years

6.4. Special conditions for storage

Cerebrolysin must be stored at room temperature (not exceeding 25° C) and protected from light (in the carton). Do not freeze. Remove the solution from the vials/ampoules immediately before use.

6.5. Nature and contents of the container

Cerebrolysin 5 ml: 5 ampoules of 5 ml

Cerebrolysin: 10 ml: 5 ampoules of 10 ml

6.6. instructions for use / handling

When Cerebrolysin is administered via a long-term intravenous catheter, the catheter has to be rinsed before and after the application with physiological sodium chloride solution. For single use only.

Use only dear, amber solutions.

7.MANUFACTURER

EVER Neuro Pharma GmbH. A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

November 2021

EVER
NEURO PHARMA