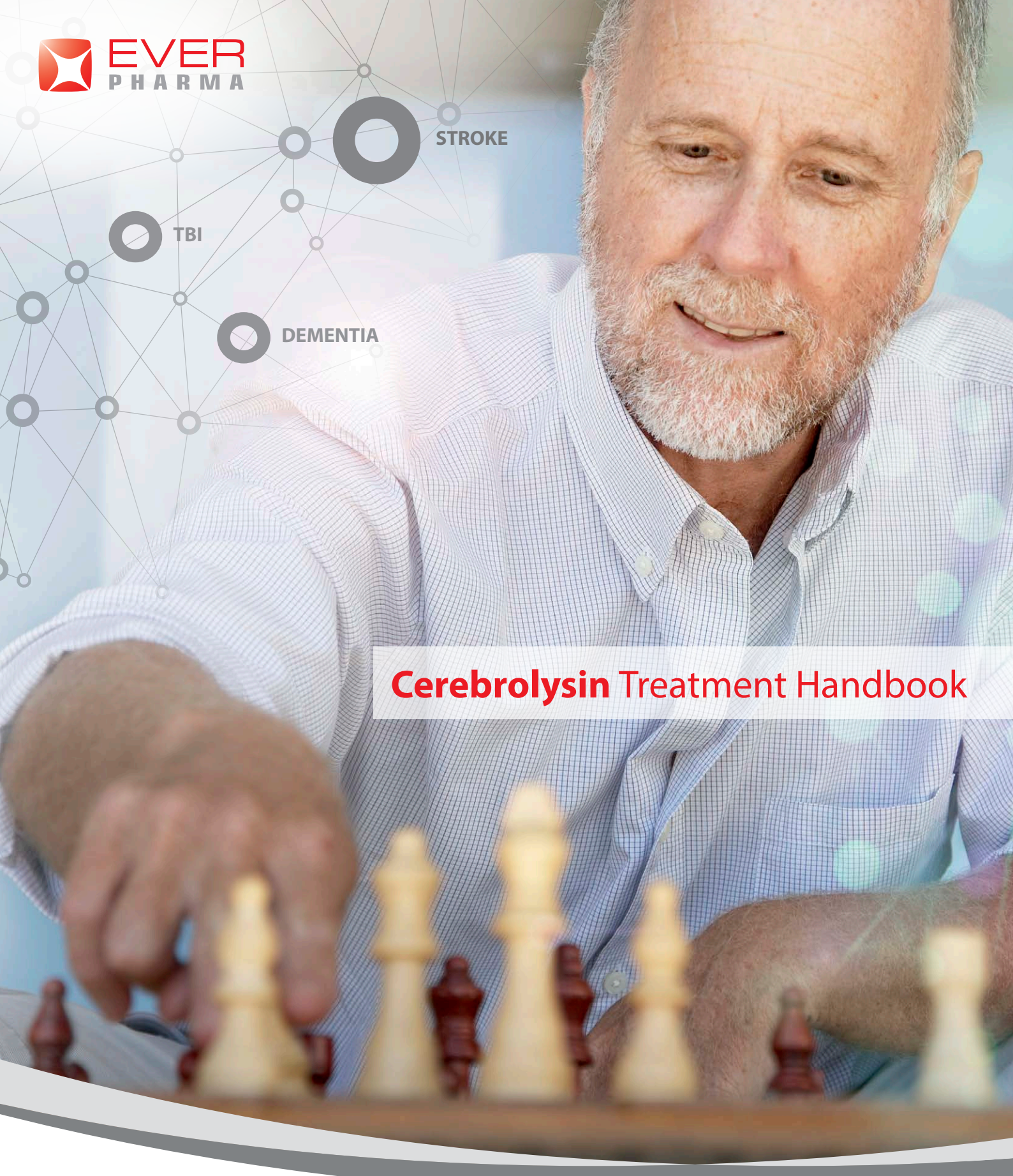
EVER PHARMA

STROKE

TBI

DEMENTIA



Cerebrolysin Treatment Handbook

Cerebrolysin®

Reconnecting Neurons.
Empowering for Life.

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HANDLING OF CEREBROLYSIN

1. DOSAGE REGIMEN

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Stroke	20 - 50 ml	as soon as possible	10 - 21 days
Traumatic brain injury	20 - 50 ml	as soon as possible	7 - 30 days
Alzheimer's disease	10 - 30 ml	as soon as possible	1 cycle: 5 days weekly/4 weeks 2 - 4 cycles per year
Vascular dementia	10 - 30 ml	as soon as possible	1 cycle: 5 days weekly/4 weeks 2 - 4 cycles per year

Daily practice experience

At what age is a treatment with Cerebrolysin possible?

There are experience reports from various countries, where Cerebrolysin is used already in infants when pediatric neurological problems are diagnosed.

Daily practice experience

How long can a Cerebrolysin treatment be given after a Stroke or TBI?

There are no limitations from pharmacological perspective.

Daily practice experience

If a patient arrives in the evening, when should Cerebrolysin be administered?

The first dose of Cerebrolysin should be applied as soon as possible, even at night. Afterwards an administration in the morning is preferable, as an infusion with Cerebrolysin is stimulating and may cause excitability.

2. INSTRUCTIONS FOR USE AND HANDLING

- **Only for single use (do not store and do not use residual content)**
- Use only clear, amber solutions
- 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
- Remove the solution from the ampoules immediately before use because microbial contaminants may grow in Cerebrolysin once an ampoule is opened
- Special precautions to avoid contamination and to guarantee sterility must be taken during the dilution and administration of Cerebrolysin:
  - Inject directly or infuse immediately
  - If Cerebrolysin has been stored in the refrigerator, allow the solution to warm to room temperature before opening the vial
  - NEVER BREAK AMPOULE if it will not be administered to the patient immediately
  - Do not leave an open ampoule on the treatment table **(bedside preparation only)**
  - To guarantee sterility, always use disposable one way IV infusion sets and cannulas
  - Discard IV lines, syringe and soluset after each application
  - Flush the IV infusion set and cannula before and after infusion with 0.9% NaCl solution

3. ROUTES OF ADMINISTRATION

Intravenous (IV) infusion	10 ml - 50 ml	diluted to at least 100 ml total volume with Saline, Ringer solution or 5% glucose solution	Infuse within 15 – 60 min
To guarantee sterility, always use disposable one-way infusion sets and cannulas! Start the infusion immediately after dilution!			

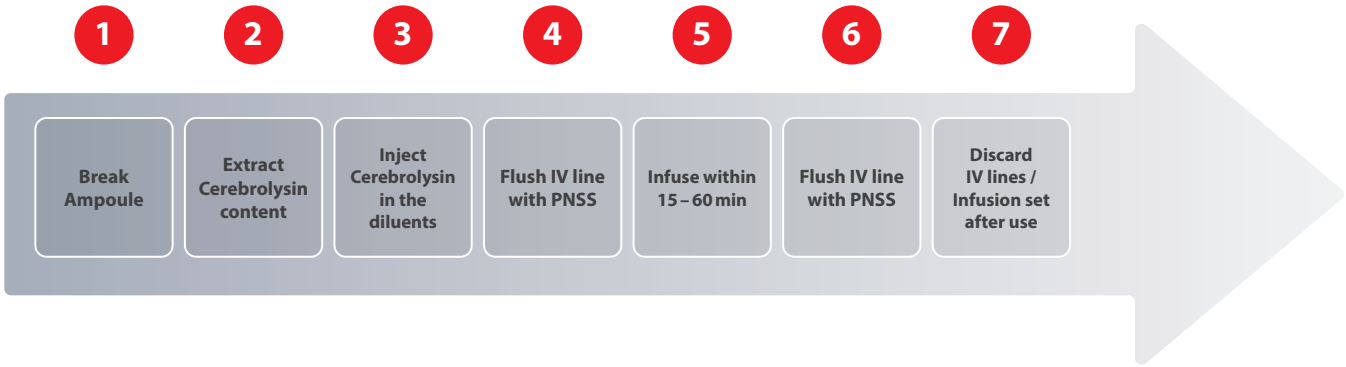
Intravenous (IV) injection	up to 10 ml	undiluted	inject slowly over 3 minutes
Intramuscular (IM) injection	up to 5 ml	undiluted	inject slowly over 3 minutes
The IV or IM injection has to be administered immediately after opening the ampoule!			

3.1. INFUSION

- Dosages between **10 ml up to a maximum of 50 ml Cerebrolysin** are recommended only as a slow intravenous infusion
  Note: Best experience has been made with 30 – 45 min infusion time of a 100 ml solution - but no longer than one hour
- Dilution has to be prepared with the suggested **standard infusion solutions**
  e.g. 0.9% sodium chloride solution, Ringer's solution, 5% Glucose
- Standard infusion solution should be **100 ml***
- Always use only disposable **on-way IV infusions sets** and cannulas
- Before starting the infusion, **flush** the infusion lines prior to use with 0.9% NaCl solution (PNSS - plain normal saline solution)
- When Cerebrolysin is administered via a **long-term IV catheter**, the catheter has to be rinsed before and after the application with physiological sodium chloride solution
- Infuse the diluted Cerebrolysin solution **within 15 to 60 minutes** (start as quickly as possible after dilution)
- Cerebrolysin can be used with other pharmacological agent but **not be mixed** in a single infusion

Amendment:
Several studies have been performed testing Cerebrolysin in combination with various standard therapies like tPA or donepezil. Most stroke patients receive other medications like statins, aspirin, NOACs, etc. during the acute or sub-acute phase after stroke. No incompatibilities have been reported.

IV Infusion - How it is administered



Safe Administration - Sterility Aspects

Special precautions to guarantee sterility must be taken during dilution and administration of Cerebrolysin:

- Remove solution from ampoules immediately before use
- Prepare at bedside! Do not leave an open ampoule on the treatment table
- Always use only disposable one-way IV infusions sets and cannulas
- When Cerebrolysin is administered via a long-term IV catheter, the catheter has to be **rinsed before and after the application with physiological sodium chloride solution**
- Pay special attention to recommended infusion/injection times

Daily practice experience

10 ml (IV) three times per day versus 30 ml (IV) administration once a day:

Both is feasible and efficacious. No difference in the efficacy is known.

An administration in the morning is preferable, as an infusion with Cerebrolysin is stimulating and may cause excitability.

Daily practice experience

Handling of Butterfly needle

IV injection or IV infusion should have pre- and post treatment flushing with a plain normal saline solution (PNSS).

As a standard in warmer countries, a saline lock* (a peripheral intravenous cannula) is used and should be changed every three days.

Hands-on-experiences by nurses show a preference for exchanging the IV line every day to prevent the possibility of contamination if a saline lock* (a peripheral intravenous cannula) is used.

Especially in countries with higher temperatures it is very important to maintain the sterility, as Cerebrolysin is a biological compound and needs to be treated sensitively.

3.2. INJECTIONS

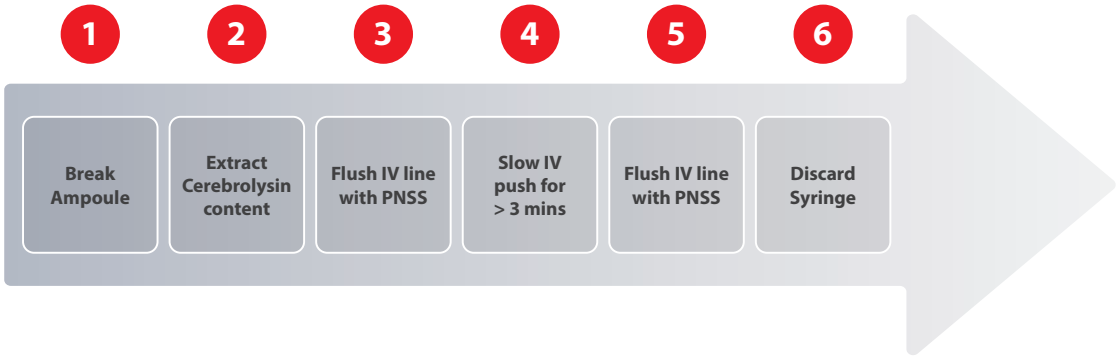
3.2.1 INTRAVENOUS INJECTION (IV PUSH)

Up to 10 ml Cerebrolysin can be injected undiluted through direct IV injection over 3 minutes.

Administer immediately after opening the ampoule.

Before and after injection flush with 0.9% NaCl solution to check if the passages are open.

IV Injection (IV Push) - How it is administered



3.2.2 INTRAMUSCULAR INJECTION

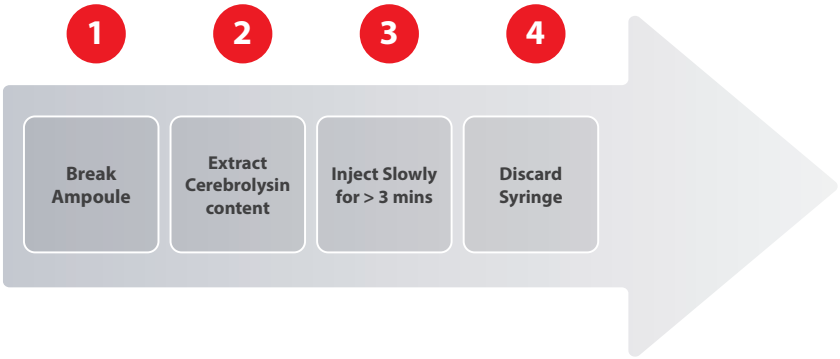
Up to 5 ml* Cerebrolysin can be administered intramuscularly over 3 minutes

Administer immediately after opening the ampoule

Before and after injection flush with 0.9% NaCl solution

Do not cool the site of injection after Cerebrolysin IM administration

IM Injection - How it is administered



Daily practice experience

Equivalence of effectiveness and safety when administered (IV versus IM)

As shown in clinical trials an intravenous route of administration with Cerebrolysin is a safe and effective treatment.

Cerebrolysin administered intramuscular is also a feasible and safe option.

No direct comparable data for IV versus IM administration are available right now.

Daily practice experience

Intramuscular treatment – Higher dosages than 5 ml per day

Intramuscular injections into different muscles or at different times may also be given to achieve the desired daily dosage.

4. STORAGE CONDITIONS

Special conditions for storage

- Cerebrolysin must be stored at room temperature not exceeding 25°C
- Do not freeze Cerebrolysin!
- If Cerebrolysin has been stored in the refrigerator, allow the solution to warm to room temperature before opening the vial
- Cerebrolysin has to be protected from light (in the carton)
- Shelf life
- Pay attention to the shelf life (5 years)

5. SPECIAL WARNINGS AND RISK OF INTERACTION

Contraindications: Administration is not recommended if the patient suffers from:

- *Hypersensitivity* to the active ingredient or another component of the drug (Sodium hydroxide and water for injection purposes)
- *Status epilepticus*
- *Severe renal failure*

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, although it is important to clarify whether it is safe to do so from a psychiatric perspective. High doses of MAO inhibitors in combination with higher dosages of Cerebrolysin (≥ 30 ml)* have been reported to increase blood pressure.

HANDLING OF SPECIFIC MEDICAL CONDITIONS

HOW FEVER COULD BE AVOIDED – DEALING WITH UNEXPECTED FEVER

In **rare cases a** fever may occur, especially after stroke.

- Check the cause of the fever.
- Normally there is no reason to stop the administration of Cerebrolysin but treat the fever with antipyretic drugs simultaneously.
- If fever persists, interrupt the Cerebrolysin treatment, treat the fever, then resume the Cerebrolysin treatment.
- **In all cases the handling is very important!**
    - **Speed of administration**: Inject Cerebrolysin very slowly. If possible, reduce the infusion drip rate or dilute Cerebrolysin in a larger solution volume (If available an injectomat or infusomat could be helpful).
      Note: Best experience has been made with 30 – 45 min infusion time of a 100 ml solution - but no longer than one hour.
    - **Storage conditions:** Not exposed to light, sterile conditions, hygiene of administration. Microbiological contaminants may grow in Cerebrolysin once the ampoule has been opened.
      Therefore, special precautions to avoid contamination and to guarantee sterility must be taken during the dilution and administration of Cerebrolysin.

HOW TO HANDLE PATIENTS WITH SEIZURES AFTER STROKE OR TBI (NON EPILEPTIC PATIENTS)

Seizures after stroke/TBI are not uncommon and may occur due to changes in electrical activity in the brain. When a stroke/TBI leaves scar tissue in the brain, it can disrupt the flow of electrical activity between nerve cells and cause a seizure.

Seizures are is not a contra-indication to use Cerebrolysin.

However, if seizures occur during a Cerebrolysin treatment it should not affect therapy. Treatment can be continued. If seizures persist – discontinue Cerebrolysin for 2 to 3 days, then continue the administration.

There is no evidence, that Cerebrolysin causes seizures.

HOW THROMBOLYZED PATIENTS SHOULD BE TREATED

Thrombolyzed patients start treatment about one hour later.

HOW TO TREAT PATIENTS WITH OTHER MINOR SIDE EFFECTS

Other minor side effects could be increased heart rate, blood pressure and arrhythmia - related to the speed of administration (this is very common in IV bolous).

The advise from practice is to inject Cerebrolysin very slowly, if equipment is available via an injectomat/infusomat. Or reduce the drip rate in infusion system or dilute Cerebrolysin in a larger solution volume if possible.

Note: Best experience has been made with 30 – 45 min infusion time of a 100 ml solution but no longer than one hour.

HOW TO DEAL WITH PATIENTS SUFFERING FROM SEVERE RENAL IMPAIRMENT

For patients with "severe renal impairment" a Cerebrolysin treatment is contraindicated. Based on the classification of „severe renal insufficiency", Cerebrolysin should not be administered to patients with a GFR category stages 4 and 5. See table below.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); **Yellow:** moderately increased risk; **Orange:** high risk; **Red:** very high risk.

https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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