Scientific Symposium EVER
New Evidence for
Pharmacological Treatment in
Post-Stroke Recovery

Satellite Symposium at the 4th EAN Congress
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Program of the symposium

New Evidence for Pharmacological Treatment in Post-Stroke Recovery

Monday, 18 June 2018, 13:45-14:45 (Room: Auditorium VI)
Chairman: Andreas Bender, Germany

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Prof. Bender, the chairman of the symposium, greeted the audience and the speakers. He underlined the comprehensive character of the program and indicated that it includes both basic research and clinical data, with newly published results of meta-analysis of Cerebrolysin's RCTs in stroke.
Timing, training, and spontaneous recovery after stroke: in animals, in humans

Steven R. Zeiler
Johns Hopkins, Baltimore, MD, USA

ABSTRACT:

Background and purpose – Most functional upper extremity motor recovery occurs in the first 4 weeks after ischemic stroke both in humans and in rodent models. The majority of recovery in humans is spontaneous (i.e. occurs as a result of endogenous repair processes rather than rehabilitative interventions). However, in rodents models, spontaneous recovery is rare. In a mouse model of stroke, we tested the hypothesis that Cerebrolysin, a polypeptide preparation shown to enhance neuronal plasticity, can act early after stroke to enhance motor recovery, either spontaneous recovery or recovery associated with motor training. Methods – Adult C57Bl/6 mice were trained to perform a skilled prehension task to an asymptotic level of performance after which they underwent photocoagulation-induced stroke in the caudal forelimb area (rodent primary motor cortex). The mice were then retrained after a 7-day delay in the presence or absence of Cerebrolysin injected IV daily. Results – We have previously shown that training-associated recovery of prehension is complete if training is initiated after a 1-day delay but incomplete if training is initiated after a 7-day delay, even with additional training days. However, daily Cerebrolysin administration after stroke was associated with complete recovery of prehension by day 8 even in the absence of training. Stroke volumes were similar across all groups. Conclusions – We conclude that Cerebrolysin administration beginning during an early time window can lead to spontaneous recovery of motor function (i.e. independent of rehabilitative interventions) and that this recovery is independent of a protective effect on stroke volume. This is one of the first demonstrations of spontaneous motor recovery in a rodent. Our mouse model, with all of the attendant genetic benefits, may allow us to determine at the cellular and molecular level how behavioral training and endogenous plasticity interact to mediate recovery.
Stroke is becoming more and more a topic of common discussions between people because almost everybody can relate to stroke experience in their families. In US only, 80 bln USD are spent annually for treating the consequences of stroke. While we achieved significant progress in reducing mortality after stroke, due to the developments in the acute treatment, the survivors need rehabilitation which is a long term process requiring much more resources than the acute treatment. 65% of stroke survivors remain with persistent motor deficits (500 000 patients a year in the USA only). This is why recovery from stroke is so important. Dr. Zeiler defined the recovery as improved success at a task, but the improvement must be related to reduction of impairment, not to behavioral compensation. The plasticity appears to be a necessary component of the true recovery processes. Dr. Zeiler underlined that recanalization and neuroprotection are not the topics of his lecture, but the processes through which the brain reorganizes itself to recover the lost functions. The proportional recovery rule describes best the powerful process of self-recovery of a stroke patient (Fig. 1).

![Proportional Recovery](image)

**Proportional Recovery**

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<td>THEREFORE</td>
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**Post-Stroke Recovery**

**Humans**

![Post-Stroke Recovery](image)

**Jørgensen et al., 1999**

**Proportional and early recovery of stroke patients**

![Fig. 1 Proportional and early recovery of stroke patients](image)
Stroke patients do recover, however they recover early and most of these processes are confined to a period of 4 weeks post-stroke, especially motor recovery. The important questions is how we, the practitioners are good at helping in this natural processes and how can we influence them? The answer to this questions is unfortunately that we do nothing, said Dr. Zeiler (Fig. 2). True recovery happens, but unfortunately despite of our rehabilitation efforts.
Dr. Zeiler’s team at Johns Hopkins University is focused on developing the therapeutic strategies that could change this situation. They specifically target the short spontaneous recovery period that was until recently neglected in our rehabilitation standards which mostly focused on behavioral compensation. In designing new therapeutic approaches they use formula for recovery, a concept developed recently by Krakauer and Carmichael (MIT Press, 2017). It describes the magnitude of recovery post-stroke as dependent on residual functions remaining after the acute treatment period, behavioral input (defined by timing and dosage of rehabilitation of impaired functions) as well as the level of plasticity processes in the post-ischemic brain.

Dr. Zeiler introduced the audience to a mouse model invented in his lab for modeling the true recovery processes as well as for developing new therapeutic strategies for stroke rehabilitation. In this model, an animal learns a prehension task and develops skills allowing for reaching out of a cage and grasping a food pellet with high accuracy and reliability. Subsequently, researchers introduce a localized, precisely delivered and reproducible stroke in the motor cortex area responsible exactly for the prehension skill that the animal just developed. The researchers discovered that if animals after stroke are rehabilitated with delay of one week they recover the lost skills only slightly. However, when animals are offered rehabilitation from the second day after stroke they fully recover the lost motor skills. It seems, that some processes important for true recovery in the animal’s brain can only be utilized for rehabilitation immediately after stroke. Interestingly, this hypothesis was further confirmed in an experiment in which the animals were given a second stroke. When rehabilitated without delay, the animals fully recovered their motor skills. While obviously the second stroke did not help by itself, it restarted this early sensitive plasticity period that helped in rehabilitation of the impaired motor skills (Fig. 3).

**Fig. 3.** The sensitive recovery period after stroke is short-lived and must be utilized while it is active for the rehabilitation of lost functions
How could we implement our knowledge about sensitive recovery period and plasticity process in our human patients? asked Dr. Zeiler. We can certainly try to optimize/enhance our rehabilitation for improved timing and intensity. However, until now, this effort did not pay off. Another approach could be to find the way to stimulate the plasticity processes within the sensitive recovery period and combine this strategy with the enhanced motor rehabilitation. There are two agents available right now that seem to be good candidates for such a novel pro-recovery strategy: Fluoxetine and Cerebrolysin. The FLAME study (The Lancet, 2011) showed that patients receiving Fluoxetine tended to recover better post-stroke than the control patients did. Dr. Zeiler’s team tested this agent in their animal model and found out that delaying the rehabilitation did not stop motor recovery processes in animals that received Fluoxetine. When researchers delayed Fluoxetine administration and delayed rehabilitation, the animals did not get better. Either Fluoxetine or rehabilitation must have been given early for animals to fully recover their motor skills. This result confirmed the observation from the FLAME study in the experimental model - both Fluoxetine and motor rehabilitation influenced the sensitive recovery period post-stroke leading to full recovery, when administered without delay. Interestingly, Fluoxetine had no impact on neuroprotection and the stroke volume was in fact increased in animals treated with Fluoxetine, in spite of full recovery.
Dr. Zeiler’s team performed similar experiments with Cerebrolysin. It is well known already for years that Cerebrolysin induces plasticity processes in many experimental models. There is also extensive data available regarding the safety and efficacy of Cerebrolysin treatment of stroke patients (see Dr. Bornstein’ lecture). When animals were given Cerebrolysin immediately after stroke they recovered completely, but, interestingly, without a need for rehabilitation. This result indicates that Cerebrolysin’s mode of action is different from that of Fluoxetine, which required additional motor rehabilitation for its pro-recovery action. Moreover, unlike in case of Fluoxetine, delaying Cerebrolysin administration had no negative impact on its pro-recovery action. Cerebrolysin is the only available agent right now that is able to stimulate processes that mimic the spontaneous recovery after stroke, said Dr. Zeiler. (Fig. 4).
Also in the case of Cerebrolysin there was no impact of the treatment on stroke volume, confirming that Cerebrolysin acts at the level of repair processes, not at the level of protection against damage, in this animal model of stroke.

Dr. Zeiler summarized his lecture saying that the magnitude of true recovery post-stroke is proportional to initial damage and depends on early onset of rehabilitation and its optimal dosage. Moreover, it also depends on activity of plasticity process and the most powerful way to enhance them is through supporting actual spontaneous recovery in the sensitive recovery period. We have now the tools that could help us in enhancing spontaneous recovery of our stroke patients. Cerebrolysin is uniquely positioned as an agent of choice for this purpose.
ABSTRACT:
Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes. Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients’ deaths, rehabilitation plays an important role in stroke care. It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke. The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary endpoint. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically statistically significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach. Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary metaanalytic results were statistically significant.

Anticorrelated processes in neurobiology - possible consequences for neurorehabilitation strategies

Dafin Muresanu
Chairman Department of Clinical Neurosciences, University of Medicine and Pharmacy “Iuliu Hatieganu”, Cluj-Napoca, Romania
In his lecture, Dr. Muresanu provided theoretical background for understanding the factors of failure and success in the development of the rehabilitation strategies for stroke patients. Dr. Muresanu defined rehabilitation as a process through which each disabled person reaches the maximum physical, functional, cognitive and psychosocial recovery possible within the limits of their disability and individual biological reserve. Then, it is also important to understand how we design and conceptualize rehabilitation efforts in order to take advantage of the capacity of any patient to recover. In medicine, in general, the leading approach to design a successful therapy is based on a medical model. This model consists of several milestones, like: focus on diagnosis of illness; heavy reliance on evidence based medicine - randomized, controlled diagnostic and treatment trials; and specific treatments (medication, intervention, surgery, etc.). This approach has its limitations, too. Specifically, in the field of rehabilitation, our experience with difficulties to develop clinical effective procedures indicates that some additional factors should also be taken into account. The rehabilitation model should be more focused on activities (disability, behavior), including participation in the community and social roles. It is more about individual patient’s needs. It is in fact an interdisciplinary field relying heavily on the “team approach”. In addition

to specific treatment, it should often focus on patient’s adaptation. The real goal and challenge, according to Dr. Muresanu, is to merge effectively both approaches and to establish evidence base for personalized rehabilitation efforts.

One of the recent developments in neuroscience which helps to better understand the scientific rationale of neurorehabilitation is the concept of anti-correlation. It explains, for example, why our efforts in neuroprotection failed to deliver clinically relevant outcomes in the past decades. After an acute brain lesion there is always an endogenous continuous brain defense response consisting of two main anti-correlated sequences. An immediate one, aiming to reduce brain damage, which is called neuroprotection and relates to initial impairment observed in stroke patients. The later stage, partially overlapping with neuroprotection, aims to repair the brain damage. The repair processes are in fact a collection of several mechanisms leading to spontaneous reduction of disability after stroke. They are defined as neurotrophicity, neuroplasticity and neurogenesis and are the foundation of neurorecovery processes (Fig. 1).

Fig. 1. The anti-correlated processes of neuroprotection and neurorepair have evolved to optimally counteract the pathological events after stroke and must be targeted in a controlled way in order to support natural recovery
Anti-correlation is a regulatory mechanism that is prominently present within the central nervous system (CNS) and describes the neurorecovery processes also at the circuitry and dynamic network levels. The brain's capacity to balance the anti-correlated processes is called endogenous neuromodulation. Pro-survival signaling mechanisms are balanced against pro-death signaling mechanisms at the cellular and molecular level. Long-term potentiation versus long-term depression are balanced at the local circuits level. Finally, synchronization processes are balanced against desynchronization processes at the dynamic network level. Every level in turn comprises of several sub-levels, and each of them are characterized by a multitude of anti-correlated processes.

In the second part of his lecture, Dr. Muresanu aimed at describing how the knowledge about anti-correlation within the CNS can influence our therapeutic approaches. For example, the timing and intensity of acute rehabilitation are important issues in post-stroke rehabilitation, but remain controversial. The physical rehabilitation must be applied with caution. The lack of knowledge about current individual status of a patient can lead to additional harm when applying early mobilization concept. The solution is individualization of the therapy, and this can be increasingly done with advanced use of biomarkers, for example, using DTI for evaluation of corticospinal tract (CST) readiness in motor rehabilitation (Boyd, 2017).

Another issue pertains to the design of clinical trials which until recently were plagued with inadequate intervention-observation schemes. The focus on early intervention and on upper limb motor recovery appears to be the spot of special interest in stroke rehabilitation and much more has to be done to develop robust clinical designs in this area. In this respect the application of ARAT score as a sensitive measure of upper limb recovery has been validated by introducing the PREP algorithm for predicting the recovery potential of upper limb after stroke (Fig. 2).
"Based on the complex pathophysiological cascade associated with acute ischemic stroke, a multimodal approach targeting an array of key mechanisms appears to be a key future approach to enhance therapy."

"Perfect candidates are drugs with trophic and regenerative effects."

Stroke. 2006;37:1129-1136

The same sensitive biomarker approach was utilized for evaluation of pharmacological support of neuroprotection and recovery after stroke in the CARS trial, in which Dr. Muresanu was a principal investigator (Muresanu et al., 2017). The study investigated pharmacological support of upper limb rehabilitation using a multimodal agent - Cerebrolysin - acting at the level of both neuroprotection and long-term neurorepair processes (Fig. 3).
In the past, we used molecules with capacity to influence long-term recovery processes as neuroprotectants. Therefore, we were not able to properly measure their clinical effects. The same happened with Cerebrolysin which for a long time was employed in clinical trials with designs targeting the neuroprotection mechanisms and their potential clinical effects. The data obtained in this period gave some interesting clues about clinical impact of this multimodal agent. However, they failed to confirm unequivocal long-term benefits for stroke patients. The combination of multimodal treatment concept and motor rehabilitation of upper limb as well as choice of the sensitive ARAT score as a primary endpoint were the foundation of the novel approach utilized in the CARS trial design (Fig. 4).

Fig. 4 The CARS trial design took into account current knowledge of the optimal motor rehabilitation timing, measurement and multimodal pharmacological support.
Dr. Muresanu finished his talk by summarizing major achievements of the CARS trial, including statistically significant improvement in the combination motor rehabilitation and Cerebrolysin group, as measured with ARAT score, in comparison with the rehabilitation only group (the control group); distribution of mRS scores between the groups; Global Status at day 90 as well as favorable safety profile of the combination treatment (Fig. 5). These results for the first time show that we have in hands a multimodal agent that can support effectively motor rehabilitation after stroke.

**Fig. 5** The results of the CARS trial investigating pharmacological support of motor rehabilitation after stroke
New evidence from a recent meta-analysis in acute ischemic stroke

Natan Bornstein
Shaare Zedek Medical Center, Jerusalem, Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT:
This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. Cerebrolysin is a parenterally administered neuropeptide preparation approved for treatment of stroke. Design: All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30-50 ml Cerebrolysin once daily for 10-21 days, with treatment initiation within 72 hours after onset of ischemic stroke. Data Sources: For five studies original analysis data were available for meta-analysis (individual patient data analysis), for four studies aggregate data were used. Study Selection: The combination by meta-analytic procedures was pre-planned and the methods of synthesis were pre-defined under blinded conditions. Search deadline for the present meta-analysis was December 31st, 2016. Results: The nonparametric Mann-Whitney (MW) effect size for NIHSS on day 30 (or 21), combining the results of nine randomized, controlled trials by means of the robust Wei-Lachin Pooling Procedure [MERT], indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, P<0.0001, N=1879). The combined number-needed-to-treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full scale ordinal analysis of mRS at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favour of Cerebrolysin (95% CI 0.52 to 0.69, P = 0.0118, N = 314). Safety aspects were comparable to placebo. Conclusion: Our meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke.
The lecture of Dr. Bornstein was dedicated to results of the recent meta-analysis of randomized clinical trials of Cerebrolysin in stroke. He indicated right from the outset that these results are in line with both research and clinical data presented earlier by Dr. Zeiler and Dr Muresanu. The lecture was divided into four sections: scientific relevance, study identification, outcome and summary.

In the chain of stroke care, which is a chronic disease treatment, we have an unfortunate disconnection between clinicians and neurologists and rehabilitation while prevention, hyper acute care, acute care and community integration are better understood and controlled. Previously, we used to leave patients after stroke in bed for 1-2 weeks, but we now know that bed rest is a wrong approach to stroke rehabilitation. Bed rest reduces the likelihood of recovery in a very significant way. On the other side, we know that among the key factors influencing recovery after stroke timing appears to be the key for success (the other factors being properly addressed, like intensity, therapy and drug). This is because every stage of stroke requires separate, dedicated and properly justified therapeutic approach (Fig. 1).

**Fig. 1** The timing of rehabilitation plays a key role in the therapeutic process of stroke patients
Our special focus, therefore, should be on taking advantage of the great potential and ability of the brain to recover spontaneously in the early phase after stroke. Moreover, this narrow window of spontaneous recovery is our opportunity to develop pharmacological approaches that will support the whole rehabilitation process.

Having this in mind, we should structure our approach to interpretation of clinical data that are already available for us. We are used to the notion that the top clinical evidence is provided by randomized clinical trials (RCTs). However, recently, the hierarchy of medical evidence moved toward the meta-analyses of the randomized clinical trials (Fig. 2).

![Hierarchy of Medical Evidence - Past](image)

![The pyramid of evidence - Present](image)

**Fig. 2** The evolution of clinical evidence toward meta-analyses of RCTs
The rationale behind this development can be understood when we take into account the issues related to conducting RCTs. The RCTs have clear strengths as a source of scientific evidence, including: randomization to avoid selection bias, prospective design using controlled conditions, blinding, defined population, detailed covariate information and high integrity of data. However, they also have serious weaknesses, like: generally small sample size, protocol driven care, center and patient selection too narrowly defined, difficulty to implement while they do not always reflect real-world clinical situations, they do not analyze how drugs are actually used, and are often inhibited by high costs. In other words, the high internal validity of RCTs often does not reflect much needed external validity and this creates serious problems in successful implementation of their results in the clinical practice.

At the same time, meta-analysis became a very useful tool. It is the statistical combination of results from two or more separate randomized, controlled clinical trials into a single estimate. This methodological approach offers some important advantages, like increase in statistical power and improvement in predictive precision. This is why meta-analyses are regarded as a tool providing the highest level of evidence.

This is also why the investigators evaluating the results of Cerebrolysin in stroke used meta-analysis as a tool of choice to properly extract meaningful clinical insight from already available and published data. This was the mixed meta-analysis approach combining the individual patients data (IPD, data obtained from the study database) and aggregate data (AD; obtained from the publication or study report) (Fig. 3). This approach is characterized by favorable analytical features like broadest possible summary of clinical efficacy results and higher level of validity. The specified aim of the meta-analysis was evaluation of the efficacy and safety of Cerebrolysin in patients with ischemic stroke with focus on early neurological conditions measured with NIHSS, and on functional status using mRS. The investigators asked the question if 30 to 50 ml Cerebrolysin treatment dose, initiated within 72 hours post acute ischemic stroke and administered for at least 1 week, have an effect on early neurological status?

Methodology of meta-analysis

Patients:
- 1879 patients
- Age: 18 – 88

Inclusion criteria:
- Hemispheric ischemic stroke in the MCA territory or arterial branches of internal carotid artery
- Moderate to moderately severe stroke

Study selection:
- Randomized, double-blind, placebo-controlled, clinical studies assessing efficacy of Cerebrolysin

Treatment:
- Cerebrolysin treatment started within 72 h post stroke onset
- Cerebrolysin treatment scheme: 30 – 50 ml
- Cerebrolysin treatment duration 10 – 21 days

Primary outcome and supportive analysis:
- NIHSS (day 0 – 21)
- mRS (day 0 – 90)
- Safety

Identified studies (N=1879)

<table>
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<th>Study</th>
<th>Principle Investigator</th>
<th>(Study report)</th>
<th>First author</th>
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Fig. 3 The design of the meta-analysis of Cerebrolysin treatment of the ischemic stroke
In the primary efficacy analysis assessing early recovery after stroke at day 30 there was a significant advantage of Cerebrolysin group in comparison with placebo, as measured with NIHSS. This result indicated that patients have a 60% chance for a better outcome when treated with Cerebrolysin. This is of importance for early initiation of rehabilitation and getting a patient out of bed early. The investigators conducted also a so called “leave-one-out meta-analysis” which confirmed NIHSS results on day 30 underlining the consistency of these results (through evaluation of the impact of a single study on the whole meta-analysis).

The number needed to treat for benefit (NNT) showed how many patients need to be treated with Cerebrolysin to obtain one good outcome. It was calculated to be NNT=7.7 which is a similar result to that obtained with IV tPA. Additionally, patients treated with Cerebrolysin have 61% better chance of positive outcome than patients on placebo, as measured with mRS at day 90. The risk of death was 17% lower in patients treated with Cerebrolysin and the overall safety profile was confirmed as excellent, with no reported serious adverse events. Fig. 4 summarizes the results of the meta-analysis.

**Fig. 4** The results of meta-analysis of Cerebrolysin in the early treatment of ischemic stroke patients
Summarizing his lecture, Dr. Borstein underlined that it was the largest meta-analysis of Cerebrolysin in stroke conducted to date. It reflected the observed growing importance of meta-analysis in the scientific world and responded to this development. IPD (individual patient data) were available for the majority of studies and the findings were homogenous showing consistent superiority of Cerebrolysin. No limitations as in other recent meta-analyses were present allowing for a valid and robust methodology and evaluation of correct data. According to these results, in the clinical practice, the best effects of Cerebrolysin can be obtained when assessing its effects at day 30 indicating impact on early recovery. This is confirmed by the combined NNT for clinically relevant changes in early recovery (NNT= 7.7). The statistically significant long term benefits are observed especially in patients with higher baseline severity. There should be no doubt regarding the safety of Cerebrolysin as it was comparable to placebo with a marked tendency for reduction of death rate.
ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Cranioencephalic trauma, post-operative trauma, cerebral contusion or concussion. 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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