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Chairman: Dieter Heiss, Germany

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The clinical development for therapeutic use of Cerebrolysin in acute and subacute stroke



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ABSTRACT:

Currently, the main therapeutic approach in acute ischemic stroke (AIS) is to seek arterial revascularization, in order to restore antegrade perfusion to the ischemic territory. Reestablishing perfusion to the territory-at-risk is associated with net clinical improvement in AIS patients, and is a crucial indicator for favorable lesional and overall outcome. Final recanalization status is a strong predictor of clinical outcomes, as indicated by recent meta-analyses of thrombectomy trials.

Nevertheless, not all patients with successful therapeutic revascularization show a favorable outcome, indicating that in many cases recanalization, albeit a strong requirement, is not sufficient to generate clinical improvement. Brain tissue perfusion is an extremely complex circulatory mechanism, strongly dependent on several factors such as local microcirculatory patency, blood-brain barrier integrity and functionality, as well as collateral circulation. Therefore, it may be

argued that brain tissue post-stroke preservation and recovery can be supported, even enhanced by preservation or opening of latent collateral circuits, or by the restitution of flow through affected microvasculature.

This approach, supported by a wealth of experimental studies, requires pharmacological interventions with complex mechanisms of action, operating well beyond the classic paradigm of pleiotropic drugs that focus solely on neuroprotection. Multimodal biological agents like Cerebrolysin mirror endogenous defense processes in the brain, promoting neurorecovery in ways that may promote considerable improvement in patient outcomes, by reducing hemorrhagic transformation and by potentially expanding AIS treatment windows, when used in combination with conventional recanalization therapy.

Dr. Muresanu, the President of the European Federation of NeuroRehabilitation Societies, opened the symposium with a lecture about the current development in combination therapies and their role in the landscape of acute and subacute stroke care. After a stroke, recanalization is the first step required for the patient's recovery. However, it is often insufficient as recanalization not always lead to reperfusion. Brain tissue perfusion is not easy to achieve and depends on collateral circulation, which differs among patients, as well as on microcirculatory patency and integrity of the blood-brain barrier (BBB).

The recovery is usually better in patients with good collaterals, which act as an alternative blood supply network. Also, successful recanalization corresponds positively with collateral circulation. The rate of hemorrhagic transformation after thrombectomy is lower in such patients. The patients with poor reperfusion and poor collateral scores (0–2) have a higher incidence of parenchymal hematoma compared to those with poor reperfusion and good collateral scores (41% [9/21] versus 20% [2/10] respectively). A direct relationship between collateral status and the NIHSS score, at the time of presentation, was also reported. The volume of critically hypoperfused tissue also directly reflects poor collateral status.

Another key obstacle in achieving proper tissue perfusion is an early and fast-progressing cerebral blood vessel damage, which follows focal cerebral ischemia. This so-called downstream microvascular thrombosis (DMT), is an event associated with proximal occlusion and usually occurs in the venous compartment of the brain (in postcapillary microvessels). The microvessel lumina are obstructed with platelets, leukocytes, and fibrin-rich aggregates due to local activation of hemostasis in the ischemic microvascular bed. The resulting incomplete microcirculatory reperfusion drives infarct growth despite successful proximal recanalization and independently of the collateral status. Several known risk factors

can additionally intensify DMT, including proinflammatory or procoagulant states (e.g. diabetes mellitus, infection, dyslipidemia).

Altogether, about 25% of patients suffer from adverse consequences of incomplete reperfusion following successful recanalization. Dr. Muresanu went on to discuss the current and potential strategies rectifying this serious problem. Recent clinical experience with thrombectomy indicates that the likelihood of favorable outcomes after endovascular therapy (EVT) increases when it follows the thrombolysis with rtPA. It appears, that rtPA not only impacts the proximal arterial recanalization but also, presumably prevents or corrects other ischemia/reperfusion-related malfunction of the microcirculation. This is also the reason why combined intravenous and intra-arterial thrombolysis, as well as ultrasound-enhanced thrombolysis, are the methods used for improving the recanalization rates.

The efficacy of the rtPA greatly depends on the quantity of the thrombus and the time of treatment. The single most important shortcoming of rtPA, resulting in the narrow time window of the treatment, is a higher rate of hemorrhagic transformation in comparison with untreated patients. Increasing the safety and efficacy of rtPA through adjunct therapies is an area of potentially high impact in acute stroke treatment. The advent of endovascular thrombectomy and the ability to investigate patients in much greater detail through advanced imaging modalities created a strong argument for revisiting the neuroprotective strategies as adjunct therapies to recanalization (Neuhaus et al., 2017). These neuroprotective interventions appear to be most relevant for short-term vascular protection (e.g. 3K3A-APC, resveratrol, salidroside).

A separate adjunctive strategy relies on multimodal treatment with agents exhibiting pharmacological properties directed at the stimulation of the biological mechanisms of recovery from stroke, like Cerebrolysin (**Fig. 1**).

Fig. 1. The multimodal agent, Cerebrolysin, displays both neuroprotective and neurorestorative properties

Among the properties of Cerebrolysin deemed most relevant for acute stroke treatment are the protection of the integrity of BBB and its anti-inflammatory properties. As mentioned before, after ischemic stroke, there is a profound deposition of fibrin in the microvasculature downstream of the proximal occlusion. This leads to increased production of pro-inflammatory cytokines by the endothelial cells, microthrombosis (DMT), and the collapse of BBB. rtPA was shown to further compromise the integrity of BBB leading to increased rates of hemorrhagic transformation. In experimental models, Cerebrolysin was shown to prevent fibrin deposition, production of pro-inflammatory cytokines as well as rtPA-induced leakage of BBB. These properties suggested the high therapeutic potential of Cerebrolysin as adjunctive therapy to thrombolysis (**Fig. 2**).

Fig. 2. Cerebrolysin ameliorates negative effects of cerebral ischemia on the microvasculature, like reduction of fibrin deposition and inflammation, and protects the integrity of the BBB

The vasoprotective action of Cerebrolysin appears to be mediated by two major regulatory pathways identified in research conducted by the group of M. Chopp from the Henry Ford Hospital (Detroit, USA; **Fig. 3**). Firstly, Cerebrolysin induces the simultaneous production of angiopoietin 1 (ANG 1) and vascular endothelial growth factor (VEGF) in the cerebral endothelial cells. These molecules are pivotal for vascular stabilization and maturation, as well as for the integrity of BBB. Additionally, ANG 1 is a known restorative molecule active in the recovery processes post-brain injuries. Another mechanism relates to the induction of the microRNAs (miRs); molecules regulating gene translation processes. Certain miRs can stimulate hundreds of genes and are investigated as targets for so-called network therapy. In this treatment concept, targeting a single miR molecule can simultaneously affect various regulatory mechanisms leading to a multimodal therapeutic effect. Cerebrolysin was shown to stimulate the production of the miR 17-92 cluster through the sonic hedgehog (Shg)-dependent pathway. miR 17-92 is responsible for the concerted regulation of the endogenous neurorecovery processes, including processes of brain plasticity (e.g. axonal growth) and stabilization of complex behavioral traits (e.g. depression and anxiety).

Fig. 3. The mechanism of action of Cerebrolysin justifies its use as adjunctive therapy for recanalization after ischemic stroke

The pilot study conducted by the group of S. Lang (2013) confirmed the safety of the combination treatment rtPA plus Cerebrolysin. Additionally, the results suggested a benefit of significantly faster recovery of the patients in the combination group in comparison with the group receiving rtPA alone (**Fig. 3**). Dr. Muresanu indicated that prolonged intermittent treatment with Cerebrolysin could further benefit such patients by supporting the neurorecovery processes active in the early post-acute phase. This view is corroborated by the clinical evidence coming from studies investigating Cerebrolysin as a therapy supporting neurorehabilitation. It is also in line with the presented earlier multimodal mechanism of action of the drug and functional studies conducted in animal stroke models.

Pharmacological chances for impairment-oriented neurorehab



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ABSTRACT:

Within the last 10 years, the number of survivors after stroke and traumatic brain injury (TBI) has dramatically increased due to advances in acute medical care. Nevertheless, the question remains if we have really made progress to influence impairment by restorative strategies rather than just improving function and consecutively participation by compensatory strategies.

Are we really able to influence impairment?

First described in 2008 (Prabhakaran et al., 2008), an interesting phenomenon occurs: The spontaneous impairment recovery after a stroke at day 90 after the ictus (with or without treatment) for upper extremity was usually 70% of the maximum possible difference between an initial score and the maximum possible. There were outliers from this rule attributable to severe pathology in the primary descending motor tracts, especially the corticospinal tract. In the meantime, this proportional recovery rule was also demonstrated to apply for impairments in non-motor domains as neglect and language abilities.

If this 70% proportional spontaneous recovery is a universal rule and cannot be influenced, this, of course, would mean that impairment-oriented

rehab is not possible. The challenge is to change the slope (i.e. from 70% to 80% or more) or to make outliers inliers.

This enigma increases the need for better pharmacological options to improve impairment in the subacute stage e.g. after stroke. So far larger RCT showed evidence for impairment reduction for only 2 substances. Antidepressants were shown to be effective in the FLAME trial with fluoxetine (Chollet et al., 2011). This could however not be corroborated in subsequent trials with larger sample size using SSRIs including citalopram (TALOS trial) and fluoxetine again (FOCUS trial).

Much larger effects could be shown for the multimodal drug Cerebrolysin, a mix of neurotrophic factors. The CARS trial (Muresanu et al., 2016) documented for the first time after decades of frustrating attempts to achieve some sort of neuroprotective and/or neurorestorative effects, indicating that a multimodal drug can improve impairment after stroke. This was further corroborated in a consecutive trial (Guekht et al., 2017) and further corroborated by a meta-analysis of stroke-related trials with Cerebrolysin (Bornstein et al., 2018). The CAPTAIN trial which is looking at Cerebrolysin's effects in TBI in a multidimensional

approach is on the way. These trials certainly need further corroborations, but the available data definitely open a new window for pharmacological interventions using a multimodal substance in combination with rehabilitative treatment.

As treatment intensity is likely to be the key element for impairment reduction, we certainly have to find clever and affordable ways to increase the daily treatment time of our patients. Today, even during inpatient rehabilitation, treatment times hardly exceed three hours a day i.e. that we use only a small percentage of waking hours leaving long "idling" time not filled by any treatment. In this sense, we have to "reinvent" neurorehabilitation within this sensitive post-injury period to combat impairment with high-frequency treatments combined with neuromodulatory techniques (robot use, peripheral and central stimulation, pharmaceuticals).

Probably the most important impact in facilitating impairment reduction will, however, have clever, economically feasible approaches to increase the net number of therapy or activity hours per day by creating a true „enriched environment“ for severely impaired patients. They should enable 6-8 hours of daytime treatment to avoid leaving our patients „inactive and alone“ in the future.

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In contrast to the progress made in the acute stroke treatment, as summarized by Dr. Muresanu, the current rehabilitation procedures have a disappointingly modest effect on impairment early or late after stroke. Irrespective of our efforts the stroke patients tend to recover in a similar fashion which conforms with the proportional recovery rule (PRR). The majority of patients (70%) achieve 80% recovery of the lost motor functions, depending on the level of initial impairment. Two therapeutically relevant questions relate to this situation: how to help non-recoverers (mostly, severe stroke patients) and how to extend functional benefit above the 80% recovery threshold? Among the treatment options considered for challenging the reality of recovery pattern, are pharmacological interventions and various stimulation techniques (of the brain or the peripheral CNS).

Up to now, only two types of substances have shown some positive signals of efficacy in decreasing impairment in the post-acute phase of stroke when administered in combination with physiotherapy. The antidepressants, like fluoxetine (SSRI), have been studied in several

trials. While the FLAME trial (Chollet et al., 2011) showed some encouraging effects on the functional outcome, as measured with mRS on day 90, the citalopram's TALOS trial (Kraglund et al., 2017) and the FOCUS trial (Dennis et al., 2018) failed to confirm these results.

Another substance studied in the context of rehabilitation is Cerebrolysin. Dr. Hömberg was directly involved in the CARS (Cerebrolysin And Recovery after Stroke) trial. This was a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group clinical study aiming to compare the effects of 30 ml Cerebrolysin (daily) versus Placebo during early rehabilitation in patients after supratentorial ischemic stroke. 208 patients were screened, enrolled, randomized and treated with the study drug (for 21 consecutive days) at 11 study centers located in Romania, Ukraine and Poland (EudraCT-2007-000870-21). The Action Research Arm Test (ARAT), a sensitive performance test for assessment of upper limb function in physical rehabilitation treatment and research, was used as a primary outcome measure (**Fig. 1**).

Fig. 1. The CARS study: the primary and secondary results

The results of the trial exceeded the expectations of the investigators. Both, ARAT score and the global score were positive, indicating the significant treatment effect of the combination of motor rehabilitation and Cerebrolysin. There was a significant shift between severity categories as measured with mRS, with 72.5% patients treated with Cerebrolysin achieving improvement in comparison with 43.8% in the Placebo group. Another group of investigators was looking for confirmation of these results. The following CARS II trial (Guekht et al., 2017) gave an inconclusive clinical recovery picture. Similarly to some previous efforts (e.g. CASTA trial), the mild stroke population included in the trial resulted in the ceiling effect of the spontaneous recovery. This, most probably, masked the impact of the combination therapy.

These generally encouraging results prompted the comprehensive meta-analysis of nine Cerebrolysin trials in stroke (**Fig. 2**). It was conducted by the group of researchers under the direction of Prof. Natan Bornstein (2018). Altogether, 1879 patients (18–88 years old) with hemispheric ischemic stroke in the MCA territory or arterial branches of the internal carotid artery were included. The patients' population represented moderate to moderately severe stroke cases. The studies selected for the meta-analysis were randomized, double-blind, placebo-controlled designs assessing the efficacy and safety of Cerebrolysin. The treatment regimens included an infusion window of 72 h post-stroke, 30–50 ml daily dose, and a duration of 10–21 days. The primary outcome and supportive analyses included NIHSS (MW) at day 30 (or 21), mRS at day 90, number needed-to-treat for the benefit (NNT, measured by NIHSS) and safety of the treatment.

Fig. 2. The meta-analysis of Cerebrolysin trials in stroke

The results showed that patients have a 60% better chance for the improved outcome when treated with Cerebrolysin (as measured with NIHSS) in comparison with Placebo. The calculated value of NNT 7.7, for clinically relevant benefits, was fairly good (95% CI 5.2-15.0). The treated patients have better chances to regain full independence (measured with mRS at day 90) as well as an increased chance of survival. The superiority of Cerebrolysin over Placebo in the improvement of neurological functions (NIHSS; MW 0.60) and the functional outcome (mRS; MW 0.61 in moderate to severe patients; $p=0.012$) was also confirmed. Larger effect sizes were observed in more severely affected stroke patients (MW 0.64 vs. 0.54). All sensitivity analyses supported the first-line results and the positive benefit-risk ratio for Cerebrolysin. This work confirmed the hypothesis formulated earlier that the more severely affected patients tend to benefit more from Cerebrolysin treatment. When discussed from the standpoint of challenging the proportional recovery rule, these results support the argument for using Cerebrolysin as adjunctive pharmacotherapy during rehabilitation after stroke.

This line of thinking was tested in another study which was not included in the meta-analysis. The ECOMPASS study (Chang et al., 2016), investigated the efficacy and safety of Cerebrolysin supporting the rehabilitation of motor function. It was a randomized, placebo-controlled, double-blind, multicenter trial that included 70 extremely well-characterized stroke patients (35 Cerebrolysin vs. 35 Placebo). All patients participated in an accompanying standardized rehabilitation program for 21 days. The primary study endpoint was day 29, patients were followed up until day 90 and were evaluated using the Fugl-Meyer Assessment (FMA). The supporting imaging analysis (rsfMRI and DTI) gave additional valuable insight into the mechanisms through which Cerebrolysin impacts the motor rehabilitation of stroke patients (**Fig. 3**).

Fig. 3. The ECOMPASS study shed a light on the stimulation of plasticity processes by Cerebrolysin leading to the recovery of motor functions

Dr. Hömberg finished his lecture by mentioning a novel approach in conducting traumatic brain injury trials. This is just another example in efforts to establish a reliable and safe pharmacological protocol supporting recovery from difficult-to-treat brain injuries. The CAPTAIN trial series is a randomized, double-blind, placebo-controlled, multi-center, multinational design investigating the effects of Cerebrolysin on neuroprotection and neurorecovery after TBI. The protocol uses a multidimensional ensemble of outcome scales. It is the first TBI trial with a 'true' multidimensional approach based on full outcome scales while avoiding prior trial design weaknesses, such as loss of information through "dichotomization," or unrealistic assumptions such as "normal distribution." After decades of unsuccessful TBI trials, the CAPTAIN series showed, for the first time, that effective and safe treatment of TBI patients is possible.

The presented overview of clinical investigations indicates that impairment-oriented neurorehabilitation requires a multimodal therapeutic approach combining the pharmacological stimulation of the biological recovery process and the task-oriented motor rehabilitation. The comprehensive multi-domain assessment of treated patients supported by the multivariate statistical analysis (Wei-Lachin procedure) is a prerequisite for successful interpretation of the results of the clinical trials.

New hope for chronic stroke patients – The IMPULSE study



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ABSTRACT:

Stroke is the leading cause of long-term disability worldwide. The immense burden of stroke-related disability demands for new approaches in neurorehabilitation. Encouraging results have been reported by noninvasive brain stimulation (NIBS), specifically transcranial direct current stimulation (tDCS), which modulates cortical excitability to facilitate motor learning. The neurotrophin BDNF (brain-derived neurotrophic factor) is seen as a relevant effector of tDCS due to its role in synaptic plasticity, learning and memory. In line, anodal tDCS (atDCS) over M1 induces a form of long-term synaptic plasticity that requires activity-dependent BDNF secretion.

Cerebrolysin is a neuropeptide preparation that has shown to promote motor recovery in stroke patients and to increase BDNF levels in patient sera. Animal models have shown increased neuronal sprouting and synaptic plasticity after Cerebrolysin administration.

In the IMPULSE study, we hypothesize that the combination of Cerebrolysin and atDCS will enhance the therapeutic benefit of a concomitant neurorehabilitation program, which includes a conventional rehabilitation protocol and task-oriented training. The IMPULSE study is a prospective, multi-center, randomized, double-blind study to assess efficacy and safety of neuroplastic intervention by Cerebrolysin and atDCS on motor function recovery in subacute and chronic stroke patients. The study will be performed at seven Austrian stroke centers with the first patient being enrolled in October 2019. IMPULSE is part of VASCage-C, a competence center of the COMET program supported by public funding.

Dr. Winkler, the Medical Director of the largest neurorehabilitation center in Austria, is continuously interested in the development of new therapies bringing benefits in post-acute stroke patients. The area of his particular interest is the multimodal approach combining various means of rehabilitation, pharmacological interventions, and novel brain stimulation technologies.

The chronic stroke patients present a large proportion of the stroke population as 80-90% of all stroke patients do not benefit from thrombolysis and thrombectomy (e.g. due to ineligibility or failed reperfusion). The challenges of rehabilitation are a multitude and aggravated by narrow time windows for the known effective interventions (**Fig. 1**).

For example, the period of increased endogenous plasticity after stroke is relatively short while most of the patients enter the rehabilitation center after its expiration. Therefore, it is very important to develop effective methods of plasticity stimulation in the chronic phase of the stroke. Another challenge is to develop therapeutic means for the recovery of lost functions (reduction of impairment). The general picture of the recovery after stroke follows the proportional recovery rule (PRR), as described for motor functions, and our failure to push recovery beyond this physiological limitation is illuminated by current rehabilitation efforts. The compensation-directed schemes, which constitute the state-of-the-art, should be viewed as the ultimate stage of rehabilitation when the reduction of impairment is no longer possible. Although work in preclinical animal models has been pivotal in highlighting the biological basis of spontaneous recovery and reduction of impairment (e.g. Zeiler et al., 2016), the translation of this knowledge into effective rehabilitation protocols has not been accomplished. In this context, the idea of testing novel therapeutic approaches allowing for re-induction of plasticity processes in the chronic stroke patients appears to be justified (**Fig. 2**).

Fig. 1. The challenges of chronic stroke rehabilitation

Fig. 2. The scientific principles of a clinical protocol for inducing plasticity in chronic stroke patients

Dr. Winkler indicated that an optimal clinical protocol for chronic stroke patients should take advantage of both spontaneous biological recovery and experience-dependent plasticity. In both cases, the neurotrophic regulation plays an important underlying role. Additionally, the stimulation of Hebbian and non-Hebbian learning processes using transcranial direct current stimulation (tDCS) can impact experience-based plasticity and also spur the spontaneous recovery

through further neurotrophic activation. tDCS was shown to induce synaptic plasticity that mimics the long-term potentiation, which is critical for learning, neuroplasticity, and rehabilitation. It is a safe and simple method of choice within the neurorehabilitation setting. In vitro and in vivo studies showed that tDCS acts through NMDA receptor- and BDNF- dependent pathways (**Fig. 3**).

Fig. 3. tDCS stimulates plasticity through BDNF-dependent neurotrophic pathway

Immediately after the stroke, and also in the early period of spontaneous recovery, the levels of BDNF (brain derived neurotrophic factor) are increased, while in severe stroke patients and the chronic phase BDNF levels are diminished. It was also determined that a critical BDNF-level is a prerequisite for inducing synaptic plasticity.

Another key component of the clinical protocol for stimulation of plasticity in chronic stroke patients is pharmacological intervention with a multimodal agent, Cerebrolysin. It is a biotechnological compound that consists of short neuropeptides which, in various experimental models, mimicked the activity of neurotrophic factors and also enhanced their levels, including BDNF levels. Recently, Steven Zeiler's group from Johns Hopkins University reported that

Cerebrolysin can induce spontaneous motor recovery in the mouse stroke model (Zeiler et al., 2018). Cerebrolysin is used for the treatment of various neurological diseases, including stroke, and is also listed in the Austrian Rehabilitation Guidelines (**Fig. 4**).

The overlap of tDCS' and Cerebrolysin's mode of action in the stimulation of plasticity led to the idea of combination treatment employing these two approaches together with the intense motor rehabilitation.

The exploratory analysis was conducted, in the Clinic Pirawarth, on 44 chronic stroke patients (>4 weeks after stroke) with impairment of upper extremity motor function. It revealed that such a combined triple therapy protocol is feasible and safe. The patients (age 18-80y) included in the

Fig. 4. Cerebrolysin, a compound recommended by the Austrian Rehabilitation Guidelines, stimulates plasticity through the multimodal neurotrophic pathway

study presented with SAFE >4 (for confirming the integrity of corticospinal tract) and ARAT >12 (for confirming the at least residual motor control of the upper arm) scores and suffered from sub-cortical ischemic stroke. Three study arms were employed. Group A received daily task-specific training (minimum 30 minutes 5 days/week) over 2 weeks. Group B received daily task-specific training plus anodal tDCS (20 minutes, 5 days a week) over 2 weeks. Group C received the triple-therapy: daily task-specific training (minimum 30 minutes

5 days/week), anodal tDCS (20 minutes, 5 days/week) and daily administration of Cerebrolysin 30ml iv over 2 weeks. The primary endpoint was the Action Research Arm Test (ARAT) score on day 14, determined as a proportional recovery score (PPR%). The results confirmed the efficacy signal of the combination treatment with the triple-therapy (group C) exhibiting the highest therapeutic impact on upper limb motor recovery (**Fig. 5**).

Fig. 5. The results of the exploratory study of triple-therapy employing Cerebrolysin, tDCS and motor rehabilitation in chronic stroke patients

The positive results of the exploratory trial encouraged the investigators to conduct further research. Dr. Winkler went on to present the protocol and rationale of the IMPULSE trial - a prospective, multi-center, randomized, double-blind study on the stIMulation of brain Plasticity to improve Upper Limb recovery after Stroke. The first stage of the study performed within 7 Austrian research centers (Pilot Study, phase II) will include 90 patients and began recruitment in October this year. Pending the positive results of this pilot, the second larger study (phase III) will be conducted. The IMPULSE is a publicly funded project and a part of the Austrian VASAge research program (**Fig. 6**).

Fig. 6. The overall concept and the timetable of the IMPULSE trial

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 – Craniocerebral 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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