**Memorandum on the clinical efficacy and safety of Cerebrolysin in ischemic stroke and traumatic brain injuries**

The clinical efficacy and safety of Cerebrolysin was studied in numerous clinical trials (139 clinical studies enrolling 22,675 patients, of which 5,693 participated in 47 double-blind, randomized, controlled clinical trials). Based on systematic analysis of this comprehensive dataset, including state of the art GRADE methodology, **Cerebrolysin was included in the clinical guidelines for stroke rehabilitation in leading Western countries, which are also highly relevant reference guidelines for Ukraine, as a drug that can improve restoration of the upper limb motor function, reduce the severity of stroke outcome and improve quality of life of post-stroke patients.**

**These guidelines recommendations include in particular:**

1) **Austria 2018** (Clinical Guidelines for Stroke Rehabilitation, https://www.xn--gsf-rna.at/wp-content/uploads/2016/11/Positionspapier-2018_OEGSF_neurologisch.pdf): "Cerebrolysin® (30 mL for 3 weeks or longer) improves upper limb recovery after stroke (Level of evidence: 2B)";
2) **Poland 2019** (Clinical Guidelines for Management of Acute Ischemic Stroke and Stroke Rehabilitation, https://journals.viamedica.pl/polski_przeglad_neurologiczny/issue/view/4583): Clinical trials have shown that the use of Cerebrolysin during early stroke rehabilitation improves neurological status and motor functions and may help reduce spasticity in upper limb paresis;
3) **Canada 2020** (Evidence Review http://www.ebrsr.com/evidence-review/10-upper-extremity-interventions and Stroke Rehabilitation Clinician Handbook http://www.ebrsr.com/sites/default/files/EBRSR%20Handbook%20Chapter%204_Upper%20Extremity%20Post%20Stroke_ML.pdf):
"Cerebrolysin® may improve upper limb motor function (Level of evidence 1A), activities of daily living and reduce the severity of stroke (Level of evidence 1B)";
4) **Germany 2020** (Grade 3 recommendation of the German Society for Neurorehabilitation, https://www.awmf.org/leitlinien/detail/ll/080-001.html):
"Cerebrolysin should be started as soon as possible (24 to 72 hours after stroke) and given for 21 days once daily, IV, in addition to rehabilitation measures (Level of evidence: 1B)";
5) The German guideline was published on the official website of the **Swiss Society for Neurorehabilitation** (https://www.sgnr.ch/deutsch/leitlinien/).
6) **Pan-European 2021: European Academy of Neurology and European Federation of Neurorehabilitation Societies** guideline on pharmacological support in early motor rehabilitation after acute ischaemic stroke published on June 21, 2021 in the European Journal of Neurology (https://onlinelibrary.wiley.com/doi/10.1111/ene.14936)

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**The said guideline states that:**

*"…Upon manually screening 17,969 unique database entries (of 57,001 original query results), interventions underwent meta-analysis.* ***Cerebrolysin (30 ml/day, intravenous, minimum 10 days)*** *and citalopram (20 mg/day, oral)* ***are recommended for clinical use for early neurorehabilitation after acute ischaemic stroke.***

"*Conclusions: This guideline provides information for clinicians regarding existing pharmacological support in interventions for neurorecovery after acute ischaemic stroke. Updates to this material will potentially elucidate existing conundrums, improve current recommendations, and hopefully expand therapeutic options for stroke survivors."*

The **European Academy of Neurology** is a non-profit organisation that unites and supports neurologists across Europe. Currently, 47 European national neurological societies as well as 2300 individuals are registered members of EAN. Thus, EAN represents more than 45,000 European neurologists. **NGO "Association of Neurologists, Psychiatrists and Narcologists of Ukraine" is an official member** of EAN and considers its guidelines in its operation.
The **European Federation of NeuroRehabilitation Societies (EFNR)** is an international, nonpartisan, non-denominational, nonprofit organization, dedicated to research, education, intellectual and scientific exchange, advocacy and philanthropic activities in the field of NeuroRehabilitation medicine and related professional areas of expertise. **NGO "All-Ukrainian Society for Neurorehabilitation" is an official member of EFNR** and should endorse its guidelines in its operation.

**In summary, based on the vast evidence base for Cerebrolysin, highly evidence oriented European organizations concluded that Cerebrolysin is recommended for clinical use to improve outcome of early neurorehabilitation after acute ischemic stroke.**

In addition, **in a recent review on neurorehabilitation, published in 2020 in the highly reputable journal LANCET**, Cerebrolysin is recognized as the only drug that has demonstrated efficacy in improving motor recovery of the patient after stroke (importantly in one of the landmark studies on this topic, the CARS trial, also three study centers from Ukrainian took part) (https://www.sciencedirect.com/science/article/abs/pii/S1474442219304156).

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**In addition, Cerebrolysin was also included in the clinical guidelines for the management of traumatic brain injury in leading Western countries, which are also reference guidelines for Ukraine, as a drug that can improve early recovery after trauma and improve the recovery of cognitive function and attention in patients after traumatic brain injury. In particular:**

1) **The Canadian Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI)**, updated in 2022, recommends Cerebrolysin with **level 1b evidence** as an effective treatment that can improve cognitive recovery after moderate-to-severe traumatic brain injury (https://erabi.b-cdn.net/wp-content/uploads/2021/09/ERABI-Module-6_-V15-July-25-2022.pdf)

**2) Romanian Guideline for Management of Traumatic Brain Injury** recommends the use of Cerebrolysin: in the acute phase and for long term treatment
http://www.ms.ro/wp-content/uploads/2021/04/Anexa-1_protocoale-terapeutice_25.03.2021.pdf

The latest meta-analysis of the Cerebrolysin study in post-TBI patients were published in the European Springer journal: **"Cerebrolysin after moderate to severe traumatic brain injury: prospective meta-analysis of the CAPTAIN trial series": *https://link.springer.com/article/10.1007/s10072-020-04974-6*.**
This prospective meta-analysis summarizes results from the CAPTAIN trial series, evaluating the effects of Cerebrolysin for moderate-severe traumatic brain injury, as an add-on to usual care. The meta-analysis concluded that treatment with Cerebrolysin was associated with an **improvement in overall recovery** at Day 90 post-TBI, as evidenced by a statistically significant benefit on 13 distinct clinical scales, a significant benefit in **early recovery** as early as day 10, **improved cognitive recovery, and reduced incidence of depression.** These observed clinical outcomes were discussed to speed up early recovery, reduce the time of hospital stay, improve the quality of life and recovery of patients after a traumatic brain injury.
The study authors concluded that:
"***The meta-analysis of the CAPTAIN trials confirms the safety and efficacy of Cerebrolysin after moderate-severe TBI, opening a new horizon for neurorecovery in this field. Integration of Cerebrolysin into existing guidelines should be considered after careful review of internationally applicable criteria**."*

In summary, there is a longstanding record of clinical studies assessing the clinical efficacy and safety of Cerebrolysin in Stroke and traumatic brain injuries that has been analyzed by independent scientific societies and led to strong recommendations for the use of Cerebrolysin to improve outcomes for patients.

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