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Evidence summary on cerebrolysin for adults post-ischemic stroke

Service Line	Evidence Summary
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Background

What is ischemic stroke?

Ischemic stroke is a result of the obstruction of vessels supplying blood to the brain, thereby severely reducing blood flow otherwise known as ischemia. The blocking or narrowing of blood vessels are usually caused by blood clots travelling through the bloodstream or fatty deposits building up in blood vessels and lodging in the blood vessels in the brain. This type of stroke is the most common as it accounts for about 87% of all strokes (American Stroke Association, 2023).

What is the standard of care for ischemic stroke?

There is no global standard of care as each country would have their own localized standard of care. The Stroke Society of the Philippines (SSP) (2014) presented guidelines on the pharmacological and non-pharmacological management of ischemic stroke with or without cardioembolic risk, as shown in the table below.

Table 1. Guidelines for the management of stroke in terms of severity (SSP, 2014):

	Mild	***Moderate***	***Severe***
NIHSS Score	0 - 5	6 - 21	≥ 22
Patient Characteristics	• (+) Mild pure motor weakness of one side of the body • (+) Pure sensory deficit, slurred but intelligible speech • (+) Vertigo with incoordination • (+) Visual field defects	• Awake, but (+) significant motor, sensory, language, or visual deficits. • (+) Disoriented, drowsy, or light stupor • With purposeful response to painful stimuli.	• Deep stupor or comatose ○ (+) Non-purposeful response ○ (+) Decortication, or ○ (+) Decerebration • Comatose patients with no response to painful stimuli.
Interventions	*(-) Cardioembolism:* • Aspirin 160-325 mg/day as early as possible x 14 days. • Aspirin with clopidogrel 75 mg • Ensure neuroprotection*** *(+) Cardioembolism:* • Anticoagulation ○ IV heparin, OR ○ SC low molecular weight heparin (LMWH) for high-risk recurrence • Aspirin 160-325 mg if anticoagulation is contraindicated • Ensure neuroprotection*** *(+) Infective endocarditis:* Give antibiotics and DO NOT anticoagulants.	*Regardless of cardioembolism risk* • Thrombolysis ○ Recombinant tissue plasminogen activator (rt-PA) ○ Aspirin 24 hours after rt-PA • Ensure neuroprotection*** • Start early rehabilitation once stable within 72 hours. *(+) Infective endocarditis:* Give antibiotics and DO NOT anticoagulate.	*Regardless of cardioembolism risk:* • Aspirin 160-325 mg/day. • Ensure neuroprotection*** • Early supportive rehabilitation. *(+) Posterior Circulation Strokes:* • Refer to a neurologist for cases within 12 hours of onset for evaluation and decision regarding thrombolytic therapy. • Early supportive rehabilitation *(+) Cerebellar Infarcts:* • Refer to a neurosurgeon as soon as possible. • Early supportive rehabilitation.

****Ensuring neuroprotection can be done through pharmacological (i.e., use of cerebrolysin) or non-pharmacological means (i.e., avoiding the 5 Hs: Hypotension, hypoxemia, hyperglycemia, hypoglycemia, hyperthermia)*

The SSP (2014) further explained that the use of drugs with neurorestorative and neuroprotective properties such as cerebrolysin in acute stroke should depend on the discretion of the physician. The following summary lists the guidelines of SSP on the early specific treatment of ischemic stroke:

- *Antithrombotic therapy* - The following antithrombotic drugs were listed for use in patients with ischemic stroke: aspirin, clopidogrel, cilostazol, low-molecular-weight heparin. These drugs reduced thromboembolism and recurrent stroke but potentially increased the risk for hemorrhagic stroke.
- *Neuroprotection* - Non-pharmacologic interventions are crucial and include avoiding hypotension, hypoxemia, hypoglycemia, hyperglycemia, and hyperthermia during acute stroke. Pharmacologic interventions include neuroprotective and neurorestorative drugs (*i.e., cerebrolysin, citicoline, NeuroAiD*) which may be given at the discretion of the physician.
- *Anticoagulation* - Anticoagulants are given to patients with acute cardioembolic ischemic stroke. The treatment is initiated with 600-800 units of heparin given hourly via IV infusion pump. Activated partial thromboplastin time (aPTT) is performed every 4-6 hours or as necessary to maintain aPTT levels at 1.5 to 2.5 times of baseline.
- *Administration of tissue plasminogen activator (rt-PA)* - IV rt-PA can be given to adults 18 and above diagnosed with clinical ischemic stroke causing measurable neurological deficit. Time of symptom onset should be less than 180 minutes before the start of treatment. Rt-PA is given via IV infusion at 0.9 mg/kg over 60 minutes, with 10% of the total dose administered as IV bolus.
- *Blood pressure management* - Allow for "permissive hypertension" during the first week to ensure adequate cerebral perfusion pressure, but ascertain cardiac and renal protection. Treat if systolic blood pressure >220 mm Hg or diastolic blood pressure >120 mm Hg, or mean arterial pressure >130

Current methods include the immediate treatment using thrombolytics, otherwise known as "clot-busting" drugs, to break up blood clots (*e.g., tissue plasminogen activator*). These drugs improve the chances of recovering from a stroke if administered within 3 hours of the first symptoms. Other methods include administration of other medicines, such as blood thinners. In cases of severe ischemic stroke, surgery to remove the blood clot causing the stroke may also be done (US Center for Disease Control and Prevention). Furthermore, aspirin, antiplatelets, and anticoagulants may also be given to patients to help reduce the risk of developing new blood clots in the future (UK National Health Service). Currently, there are no approved treatments for post-ischemic stroke in the WHO Essential Medicine List (WHO EML 2021).

In the Philippine National Formulary, four drugs were indicated for post-acute ischemic stroke. These include aspirin for the management of acute ischemic stroke, clopidogrel for early specific or secondary treatment of acute ischemic cerebral infarction, dipyridamole for the secondary prevention of stroke in patients with non-cardioembolic ischemic stroke, and alteplase for the management of acute ischemic stroke within 0-4.5 hours of symptom onset. However, none of these four PNF-listed drugs were mentioned to have neuroprotective / neurorestorative properties as with cerebrolysin.

What is the potential of cerebrolysin for adults post-ischemic stroke?

Cerebrolysin is a porcine brain-derived proteolytic peptide fraction that is used as a neuroprotective and neuroregenerative agent (MIMS, 2023) post-stroke. It is capable of passing intact through the blood-brain barrier. It stimulates cell differentiation, improves nerve cell function, and prompts mechanisms of protection and repair among nerve cells, particularly after marked nerve cell injury. Moreover, it enhances the expression of nerve-growth factor and brain-derived neurotrophic factor (Kang et al, 2020). Cerebrolysin is available in 215.2 mg/ampule concentrate solution for IV infusion. It is currently registered with the Philippine Food and Drug Administration (FDA).

In this review, we looked at the clinical evidence (*including the efficacy and safety*), and economic impact of cerebrolysin in combination with rehabilitation and/or standard of care (SOC) as treatment against rehabilitation and/or SOC alone among post-ischemic stroke patients.

Policy Question

Should **cerebrolysin** be included in the Philippine National Formulary for the treatment of post-ischemic stroke across different levels of severity?

Research Questions

Clinical efficacy and safety

- What is the efficacy of cerebrolysin compared with rehabilitation and/or placebo in terms of (a) early motor rehabilitation, (b) neurological function, (c) global functioning among adults post-ischemic stroke?
- What is the safety of cerebrolysin compared with rehabilitation and/or placebo in terms of (a) any adverse event, (b) all-cause death, (c) serious adverse events among adults post-ischemic stroke?

Economic impact

- What is the associated medication cost per adult with post-ischemic stroke when using cerebrolysin in combination with rehabilitation and/or SOC versus rehabilitation and/or SOC alone?
- What is the total medication cost for the expected number of adults with post-ischemic stroke using cerebrolysin in combination with rehabilitation and/or SOC versus rehabilitation and/or SOC alone?
- What is the three-year projected budget impact to the government for the expected number of adults using cerebrolysin in combination with rehabilitation and/or SOC versus rehabilitation and/or SOC alone?

Context on the assessment framework

In alignment with our methodological framework for assessment, the results of the clinical assessment will determine if the assessment shall proceed to assessment of other HTA domains. Only health technologies that will demonstrate superiority or non-inferiority versus the comparator in the clinical assessment shall proceed to economic impact assessment, as well as the ethical, legal, social and health systems impact assessment.

HTA Council Summary of Judgment

The HTAC concluded with the following findings based on its decision framework as stipulated in Republic Act 11223 or the *Universal Healthcare Act*:

Criteria	Adults Post-Ischemic Stroke
Clinical Efficacy / Effectiveness & Safety	Based on the review of clinical evidence, the relative treatment effect of cerebrolysin in combination with rehabilitation and/or standard of care (C-RS) compared to rehabilitation / SOC (RS) alone across all efficacy and safety outcomes mostly yielded non-statistically significant results (i.e., *inconclusive*). The HTA Council has therefore deemed that C-RS is **non-inferior** to RS alone for the treatment of adults post-ischemic stroke, based on moderate to very low certainty of evidence.
Cost- effectiveness	Since the clinical impact judgment is **non-inferior**, the economic evaluation was performed through cost-minimization analysis and budget impact analysis. *(Results are presented under Affordability and Viability.)*
Affordability and Viability	The estimated budget impact analysis and the costing analysis based from the computation of the HTAC showed that the government will potentially incur an additional cost of **₱25,067.25** per potential user and **₱5.15 B** for all targeted users for three years.

HTA Council Preliminary Recommendation

The HTA Council ***does not recommend government financing*** of cerebrolysin, in combination with rehabilitation, for the treatment of adults post-ischemic stroke ***through its non-inclusion in the PNF*** due to the following:

- Based on one critically low-quality review[1] (SR) that reported efficacy outcomes, it was shown that adding cerebrolysin to rehabilitation and/or SOC is clinically **non-inferior** compared to rehabilitation alone. Upon validation of quality of evidence through GRADE and ROB, the HTAD-validated GRADE ratings were generally lower than that of the SR[1].
- Based on one moderate-quality SR[2] and one high-quality SR[3], all safety outcomes were not statistically significant. Therefore, the SC deemed there **is insufficient evidence to assess** for the safety of adding cerebrolysin to rehabilitation and/or SOC.
    - Furthermore, it was found that the government will potentially incur ***additional*** costs of **₱25,067.25** per target user and an additional **₱5.15 B** for all targeted users for three years if the government will shift to this new intervention.

[1] Beghi et al (2021), [2] Strilciuc et al (2021), [3] Ziganshina et al (2020)

REVIEW OF EVIDENCE

Responsiveness to Disease Magnitude and Severity

Current prevalence/ severity of the disease

According to the World Stroke Organization (WSO), over 12.2 million new stroke cases are recorded each year. Among these, 7.6 million are considered ischemic strokes. Hence, over 62% of strokes worldwide are ischemic strokes (Global Stroke Fact Sheet, 2022).

In the Philippines, Collantes et al (2022) reported that the prevalence of stroke ranges from 0.486% to 6% among Filipinos with ischemic stroke, having a higher prevalence compared to hemorrhagic stroke. The Philippine Statistics Authority (PSA, 2022) reported both cerebrovascular diseases and ischemic heart diseases as two of the three main causes of death in the country from January to May 2022. In spite of the burden of cerebrovascular diseases, healthcare remains disproportionate with a ratio of 106 neurologists per 100,000 population, of which most are concentrated in highly urbanized areas (Collantes et al, 2022). Mortality rate from stroke is recorded to be highest in the National Capital Region (NCR) and the areas surrounding this region, while mortality rate is lowest in areas far from the NCR (*i.e., Autonomous Region in Muslim Mindanao*). However, this may be the trend in more remote regions because of lower rates of reporting, poor data management, or early death as a result of lack of facilities and expertise (Loo & Gan, 2013).

The most common complications after stroke include brain edema, pneumonia, urinary tract infection, seizures, clinical depression, bedsores, limb contractures, shoulder pain, and deep venous thrombosis (American Heart Association & American Stroke Association, 2015) Moreover, according to Zhang et al (2020, a spectrum of neuropsychiatric disorders are common complications after stroke; In terms of frequency of common neuropsychiatric disorders after stroke (NDS) Depressive disorders is 4-84%, anxiety disorders is 20-24%, as well as post-traumatic stress disorder (PTSD) 8.3-29.6%, and psychosis and psychotic disorders after stroke is 4.67-5.05% frequent/prevalent in patients who suffered stroke.

Efficacy, Effectiveness and Safety

Brief Methodology on evidence synthesis

Location and Selection of Studies

This evidence review performed a targeted search among stringent national research agencies (*i.e., CADTH, UK NICE, and PBAC*), WHO EML, MedLine via PubMed, and Cochrane without language restriction.

Critical appraisal

- *Risk of Bias Assessment for Systematic Reviews of Interventions.*
  Each RCT included in this review was assessed by the SRs using the Risk of Bias assessment (ROB I). Potential conflicts of interest were reviewed and included by the SRs as part of the ROB assessment.

- *GRADE*
  Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess the certainty of evidence. Results of each key outcome were subjected to the GRADE assessment. The outcomes were subdivided into two groups; efficacy and safety. The importance of the outcomes were then graded according to its measured ROB, inconsistency, indirectness, imprecision, and other factors were also considered such as if the study is a pre-print, large magnitude of effect, dose-response gradient, possible confounders, in adherence with the Cochrane Handbook for Systematic Reviews of Interventions using GradePro.

  Appraisal of all SRs included the extraction of the following characteristics: source, author, title, and year. After determining eligibility of studies for full-text screening, included studies were assessed for the following: author, year, title, population, intervention, comparator, outcome, and study design. Since data extraction was conducted by two independent assessors, inconsistencies in the extraction were resolved by consensus of an arbitration with the team lead.

Description of Included Studies

A systematic search was conducted to detect existing systematic reviews on the use of cerebrolysin for post-ischemic stroke patients through PubMed and a targeted search for HTA evidence review reports from the WHO, CADTH, UK NICE, PBAC, Cochrane, and submission from the manufacturer. Three latest systematic reviews (SRs) (Beghi et al, 2021, Ziganshina et al, 2020, & Strilciuc et al, 2021) were found to fit the research questions. Additional search for randomized control trials (RCTs) published after the search of these three SRs was also conducted to review if there were any new RCTs published after the SRs and with conflicting results. Based on the search performed, there are no new RCTs, implying that these three SRs are the latest valid SRs to refer to for this assessment .

Of these three, only one SR (Beghi et al, 2021) provided results for efficacy outcomes. As for the safety outcomes which were common among the three SRs, the most recent SR (Strilciuc et al, 2021) was adopted, examining four outcomes: serious adverse events (SAEs), fatal SAEs, all-cause death, and any adverse event (AE). Only one outcome (*i.e., fatal SAEs*) was unique from Ziganshina et al (2020), and thus was adopted. No additional RCTs published after the last search date of 23 January 2023 were found.

- In terms of the ***study design*** *of the included primary studies*, all three SRs included randomized controlled trials. From these three SRs, there are common RCTs included. In total, there are 12 unique RCTs reviewed through these SRs.
    - There were six pivotal trials which include: CARS (Guekht et al, 2017), CASTA (Heiss et al, 2012), CERE-LYSE (Lang et al, 2013), and E-COMPASS (Chang et al, 2016).
    - For seven RCTs (Amiri-Nikipour et al, 2014; Gharagozli et al, 2017; Ladurner et al; 2005; Shamalov et al, 2010; Skvortsova et al, 2004; Stan et al, 2017; Xue et al, 2016), pivotal trials were not named.
- In terms of the ***population***, all three SRs included adults post-ischemic stroke. Sample size ranged from 72 to 2080.
- In terms of the ***intervention***, all SRs (Beghi et al, 2021, Ziganshina et al, 2020, & Strilciuc et al, 2021) used cerebrolysin as an add-on to SOC alone (Ziganshina et al, 2020), or SOC and/or rehabilitation (Beghi et al, 2021; Strilciuc et al, 2021). The SOC used by the SRs differed: Beghi et al, 2021 used aspirin and/or neurorehabilitation; Ziganshina et al, (2020) used aspirin, saline, pentoxifylline, antilipemic agents, anti-hypertensives, hypoglycemic agents, dehydration therapy, n-butylphthalide, and thrombolytic therapy [*e.g., heparin, tissue plasminogen activators*]; Strilciuc et al (2021) used alteplase, saline + aspirin, and DL-3-n-butylphthalide and/or rehabilitation..
- In terms of the ***comparator***, Beghi et al (2021) used neurorehabilitation and/or SOC (*i.e., aspirin*) alone, initiated within the first week after stroke onset (i.e., before the early subacute stage or 7 days to 3 months). Strilciuc et al (2021) used SOC (*i.e., alteplase, saline + aspirin, and DL-3-n-butylphthalide*) and/or rehabilitation alone or with placebo. Ziganshina et al, (2020) used SOC (*i.e., aspirin, saline, pentoxifylline, antilipemic agents, anti-hypertensives, hypoglycemic agents, dehydration therapy, n-butylphthalide, and thrombolytic therapy* [*e.g., heparin, tissue plasminogen activators*]) alone or with placebo.
- In terms of the ***outcomes***, only one SR (Beghi et al, 2021) reported efficacy outcomes while all three SRs (Beghi et al, 2021, Ziganshina et al, 2020, & Strilciuc et al, 2021) reported safety outcomes.
    - *Efficacy:* Beghi et al (2021) reported outcomes on *early motor performance* , *neurological function*, and *global functional outcome* at months 1 and 3.

- *Early motor performance:* upper extremity performance (*coordination, dexterity and functioning*) in stroke recovery, brain injury and multiple sclerosis populations, measured by the Action Research Arm Test [ARAT].
- *Neurological function:* Severity of stroke which can be measured by the NIH Stroke Scale (NIHSS) at months 1 and 3;
- *Global functional outcome:* assessment of disability in individuals who suffered from stroke and is compared over time to check for recovery and degree of continued disability. This is measured by the Modified Rankin Scale (mRS).

- *Safety:* All three SRs (Beghi et al, 2021, Ziganshina et al, 2020, & Strilciuc et al, 2021) reported *serious adverse events*. Two SRs (Ziganshina et al, 2020, & Strilciuc et al, 2021) reported *any adverse event (AE), non-fatal serious adverse events*, and *all-cause death*. Only Ziganshina et al (2020) reported *fatal SAE*.
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  - For all outcomes reported by at least two SRs, the results of Strilciuc et al (2021) were adopted because it is the most recent SR and pooled the most RCTs into its outcomes.
  - One outcome uniquely reported by Ziganshina et al (2020) was also adopted.

Table 2. Distribution of Outcomes per SR

Outcomes	**SR Author (Year)**		
	Ziganshina et al (2020)	**Beghi et al (2021)**	**Strilciuc et al (2021)**
EFFICACY			
Early Motor Performance		✓	
Neurological Function		✓	
Global Functional Outcome		✓	
SAFETY			
Any Adverse Event	✓		✓
All-Cause Death	✓		✓
Serious Adverse Events (SAEs)	✓	✓	✓
Non-Fatal SAE	✓		✓
Fatal SAE	✓		

All included SRs conducted risk of bias assessment using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB-1). Only Beghi et al (2021) and Ziganshina et al (2020) assessed the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool.

Table 3: PICO of Included SRs

Study	Population	Intervention	Comparator	Outcomes	SD	AMSTAR Rating
Beghi et al (2021)	Adults who experienced ischemic stroke	Pharmacological intervention (***including cerebrolysin***) as add-on to SOC[+++] and/or neuro-rehabilitation	SOC[+++] and/or neuro-rehabilitation alone	*Efficacy* ● Early motor performance (ARAT score) ● Neurological function (NIHSS score) ● Global functional outcome (mRS score) Safety ● Serious adverse events (SAE)	SR (*within a CPG*)	Critically Low
Ziganshina et al (2020)		SOC*** + Cerebrolysin	SOC*** alone or with placebo	*Safety:* ● Total AE ● SAE ● Fatal SAE ● Non-fatal SAE ● All-cause death	SR	High
Strilciuc et al (2021)		[SOC^^^ and/or rehabilitation] + Cerebrolysin	[SOC^^^ and/or rehabilitation] alone or with placebo	*Safety:* ● At least 1 AE ● SAE ● Non-fatal SAE ● All-cause death	SRMA	Moderate

[+++]aspirin

****alteplase, saline + aspirin, and DL-3-n- butylphthalide*

^^^aspirin, saline, pentoxifylline, antilipemic agents, anti-hypertensives, hypoglycemic agents, dehydration therapy, n-butylphthalide, and thrombolytic therapy [e.g., heparin, tissue plasminogen activators]

Table 4. Comparison of RCTs in the Included SRs

RCT (Year)	Ziganshina et al (2020)	Beghi et al (2021)	Strilciuc et al (2021)
Amiri-Nikipour et al (2014)	✓	✓	✓
Chang et al (2016)		✓	✓
Gharagozli et al (2017)	✓		✓
Guekht et al (2015) in Guekht et al (2017) *Full-text inaccessible*			✓
Heiss et al (2012)	✓		✓
Ladurner et al (2005)			✓
Lang et al (2013)	✓		✓
Muresanu et al (2016)		✓	✓
Shamalov et al (2010) *Full-text translated only*			✓
Skvortsova et al (2004) *Full-text inaccessible*	✓		✓
Stan et al (2017)	✓	✓	✓
Xue et al (2016)	✓		✓

AMSTAR Rating for Systematic Reviews

The quality of systematic reviews were appraised using the *A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2)* critical appraisal tool. Details of the AMSTAR Rating can be found in Annex C.

- Ziganshina et al (2020): *High* because all domains in the AMSTAR-2 Tool have been satisfied.
- Strilciuc et al (2021): *Moderate* due to weaknesses in the following non-critical domains: Domain #3 (*i.e., no explicit explanation on why only RCTs were included in the SR*); Domain #10 (*i.e., no explicit mention of appraisal of the funding sources of the included RCTs*).
- Beghi et al (2021): *Critically low* due to weaknesses in the following critical and non-critical domains:
  - ***Critical:*** Domain #11 (*i.e., justified the combining of data in a meta-analysis but no explicit mention on the causes of heterogeneity*), Domain #15 (*i.e., no explicit mention of an examination for publication bias [e.g., Funnel Plot, Egger's test]*).
  - ***Non-Critical:*** Domain #3 (*i.e., no explicit rationale for using non-randomized studies*), Domain #10 (*i.e., no explicit mention of appraisal of the funding sources of the included RCTs*), Domain #14 (*i.e., no explicit discussion of sources of heterogeneity*)
  - Because of the appraised quality of this SR, a reassessment of risk of bias and certainty of evidence (*i.e., using GRADE*) was performed.

Table 5: Summary of AMSTAR Rating Results

Study	SD	AMSTAR Rating	
Beghi et al (2021)	SR (*within a CPG*)	**Critically Low*** **	• **With 2 critical flaws**. • Did not investigate causes of heterogeneity and no mention of examining publication bias
Ziganshina et al (2020)	SR	**High**	• **No critical and non-critical flaw.**
Strilciuc et al (2021)	SRMA	**Moderate**	• **No critical flaw, but with 2 non-critical flaws.** • No explanations for including only RCTs and on sources if funding of individual RCTs

****Because of this rating, we validated the certainty of evidence by performing a separate risk of bias and GRADE assessment for all outcomes adopted from Beghi et al (2021).*

Results of the Risk of Bias Assessment

Risk of Bias assessment (ROB I) was conducted by Strilciuc et al (2021), Beghi et al (2021) and Ziganshina et al (2020) for all studies. Each outcome from each RCT included in this review was assessed using the Risk of Bias tool version I (ROB I). Strilciuc et al (2021) performed ROB assessment for four outcomes (*i.e., SAE, non-fatal SAE, any AE, and all-cause death*), but no overall ROB was given.

The ROB assessment performed by Strilciuc et al (2021) and Ziganshina et al (2020) were deemed acceptable and consequently adopted because their AMSTAR ratings were moderate and high, respectively. However, since Beghi et al (2021) had a critically low AMSTAR Rating (*see section on AMSTAR Ratings*), ROB was reassessed by the assessment team.

- Based on the HTAD assessment of the risk of bias using ROB I, studies included by Beghi et al (2021) all had unclear ROB.
- Reasons for *Unclear ROB* rating mostly revolved around one or a combination of the following issues: *lack of blinding of assessors, selective reporting, and unaccounted participants lost to follow up*.
- In comparison to the ROB rating of Beghi et al (2021), the independent HTAD ROB appraisal of studies was generally ***lower***
  - Beghi et al (2021) rated all its included studies as having *no serious ROB*.
  - *A*ll of HTAD's ratings had *serious ROB*.
- The overall ROB ratings per outcome are summarized in Table 6.

Table 6. Independent ROB assessment of Included RCTs in the SR of Beghi et al, 2021

OUTCOME	RCT	OVERALL ROB RATING (Reason)	Converted ROB Rating in the GRADE TABLE
Early Motor Performance *Month 1*	Muresanu et al, 2016	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting)	**Serious**
Early Motor Performance *Month 3*	Muresanu et al, 2016	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting)	**Serious**
	Guekht et al, 2015	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting)	**Serious**
Neurological Function *Month 1*	Amiri-Nikipour et al, 2014	**UNCLEAR** (3 UNCLEAR ratings - unclear allocation concealment, participants lost to follow-up; selective reporting)	**Serious**
	Muresanu et al, 2016;	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**
	Guekht et al, 2015;	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**
	Stan et al, 2017	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**
Neurological Function *Month 3*	Amiri-Nikipour et al, 2014;	**UNCLEAR** (3 UNCLEAR ratings - unclear allocation concealment, participants lost to follow-up; selective reporting)	**Serious**
	Muresanu et al, 2016	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**
Global Functional Outcome *Month 1*	Stan et al, 2017	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**
Global Functional Outcome *Month 3*	Muresanu et al, 2016	**UNCLEAR** (2 UNCLEAR ratings - participants lost to follow-up; selective reporting	**Serious**

GRADE Rating of Evidence

For efficacy outcomes, while Beghi et al (2021) has already performed GRADE, a GRADE assessment was performed independently for validation purposes, in light of the *critically low* AMSTAR rating of this SR

For safety outcomes, on the other hand, the GRADE rating for fatal SAEs was adopted from Ziganshina et al (2020). Since Strilciuc et al (2021) did not conduct GRADE, the assessment team for this review performed GRADE for four outcomes (*i.e., SAEs, non-fatal SAEs, any AE, and all-cause death*), with ROB results adopted from Strilciuc et al (2021).

- Based on the HTAD assessment of the certainty of evidence using GRADE for outcomes adopted from Strilciuc et al (2021) and Beghi et al (2021), the certainty of evidence for all outcomes of the included studies ***ranged from very low to moderate certainty of evidence.***
- Reasons for a ***very low*** certainty of evidence were mostly due to the following reasons:
    - Beghi et al (2021)*:* Serious risk of bias due to unclear missing outcomes and selective reporting (*i.e., unable to countercheck figures due to irretrievable protocol*), and unclear allocation concealment; and very serious risk of imprecision (*i.e., wide CI, crossing the null*)
    - Strilciuc et al (2021): Serious risk of bias due to unclear allocation concealment and blinding of participants, healthcare providers, and outcome assessors; and very serious imprecision (*i.e., wide CI, crossing the null*)
- Reasons for ***low*** certainty of evidence were mostly due to the following reasons:
    - Beghi et al (2021)*:* Serious risk of bias due to unclear missing outcomes and selective reporting (*i.e., unable to countercheck figures due to irretrievable protocol*), and unclear allocation concealment; and serious risk of imprecision (*i.e., wide CI*)
    - Strilciuc et al (2021): Serious risk of bias due to unclear blinding of participants, healthcare providers, and outcome assessors; and serious risk of imprecision (*i.e., crossing the null*)
- ***Moderate*** certainty of evidence was given for the outcome of fatal *adverse events* in Ziganshina et al, 2020 because of serious risk of bias (*i.e., incomplete outcomes, unclear blinding of assessors, unclear allocation concealment, unclear selective reporting*) .
- In comparison to the GRADE rating of Beghi et al (2021), the independent HTAD GRADE Rating of studies was generally ***lower***.
    - Beghi et al's (2021) certainty of evidence ranged from low to high, with most outcomes having a high rating.
    - HTAD's certainty of evidence ranged from very low to low, with most outcomes having a low rating.

Results on Efficacy

*NOTE: RCTs in red font have **inaccessible full-text articles.***

Out of the three included SRs, only Beghi et al (2021) provided results for efficacy outcomes. Of these results, three of six outcomes (*early motor performance [month 3], neurological function [months 1 and 3]*) were pooled by Beghi et al (2021). The remaining three outcomes (*early motor performance [month 1], global functional outcome [months 1 and 3]*) were not pooled because each outcome was reported only once. *Early motor performance [month 1*] and *global functional outcome [month 1] w*ere reported by Muresanu et al, (2016), while *global functional outcome [month 3]* was reported by Stan et al, (2017).

Among the six efficacy outcomes, five outcomes (*i.e., early motor performance [month 1], neurological function [months 1 and 3], and global functional outcome [months 1 and 3]*) provided results in favor of cerebrolysin (*low certainty of evidence*). Only one outcome (*i.e., early motor performance [month 3]*) provided inconclusive results (*very low certainty of evidence*).

Efficacy Outcome 1 and 2: Early Motor Performance 1 and 3 months after stroke

Beghi et al (2021) assessed the early motor performance (EMP) of cerebrolysin + neurorehabilitation vs. neurorehabilitation alone using the Action Research Arm Test (ARAT) at months 1 and 3 after stroke. ARAT is a 19-item observational test used for the assessment of upper extremity performance (*i.e., coordination, dexterity and functioning*) in stroke recovery (Physiopedia, n.d.; Yozbatiran, Yeghiaian, & Cramer, 2008).

- *EMP at Month 1:* The odds of improved early motor performance at month 1 after stroke is 135% higher in the cerebrolysin group when compared with neuro-rehabilitation alone (*OR: 2.35; 95% CI: 1.43 to 4.04*) based on the results of one RCT (Muresanu et al, 2016) as adopted by Beghi et al (2021). The overall certainty of evidence was ***low*** because of a serious risk of imprecision (*wide CI*) and serious ROB (*i.e., unclear missing outcomes and selective reporting due to irretrievable protocol*).
- *EMP at Month 3:* At month 3 after stroke, the odds of improved early motor performance is not statistically significant (*i.e., inconclusive*) in the cerebrolysin group when compared with neuro-rehabilitation alone (*OR: 2.12; 95% CI: 0.68 to 6.59; I^2=89.40%*), based on the results of two RCTs (Muresanu et al, 2016; Guekht et al, 2015) as pooled by Beghi et al (2021). The overall certainty of evidence was ***very low*** with a very serious risk of inconsistency and imprecision, and serious ROB (*i.e., unclear missing outcomes and selective reporting due to irretrievable protocol*).

Efficacy Outcome 3 and 4: Neurological Function (NF) 1 and 3 months after stroke

Beghi et al (2021) assessed this outcome using the NIH Stroke Scale (NIHSS) at months 1 and 3 after stroke. The NIHSS is an 11-scale tool used to measure stroke-related neurological deficits. It is used in clinical practice to evaluate and document neurological status in acute stroke and determine appropriate treatment for stroke patients (Physiopedia, n.d.; AHA, 2017).

- *NF at Month 1:* Based on the results of four RCTs (Amiri-Nikipour et al, 2014; Muresanu et al, 2016; Guekht et al, 2015; Stan et al, 2017) as pooled by Beghi et al (2021), the odds of improved neurological function at month 1 after stroke is 94% higher in the cerebrolysin group when compared with neuro-rehabilitation alone (*OR: 1.94; 95% CI: 1.35 to 2.77; I^2=18.08%*). The overall certainty of evidence was ***low***, with serious risk of imprecision (*wide CI*) and serious risk of bias (*i.e., unclear selective reporting due to irretrievable protocol; unclear allocation concealment*).
- *NF at Month 3:* Based on the results of two RCTs (Amiri-Nikipour et al, 2014; Muresanu et al, 2016) as pooled by Beghi et al (2021), the odds of improved neurological function is

267% higher in the cerebrolysin group when compared with neuro-rehabilitation alone (*OR: 3.67; 95% CI: 1.89 to 7.13; I^2=28.72%*). The overall certainty of evidence was ***low***, with serious risk of imprecision (*wide CI*) and serious risk of bias (*i.e., unclear missing outcomes and selective reporting due to irretrievable protocol; unclear allocation concealment*)**.**

Efficacy Outcome 5 and 6: Global Functional Outcome (GFO) 1 and 3 months after stroke

Lastly, Beghi et al (2021) assessed global functional outcome using the modified Rankin Scale (mRS) The mRS is a six-category tool which measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. (Swieten, n.d.; AHA, 2007)

- *GFO at Month 1:* Based on the results of one RCT (Stan et al, 2017) as adopted from Beghi et al (2021), the odds of improved global function is 352% higher in the cerebrolysin group when compared with neuro-rehabilitation alone in after 1 month in medication after stroke (*OR: 4.52; 95% CI 1.88 to 14.93*). The overall certainty of evidence was ***low***, with serious risk of imprecision (*wide CI*) and serious risk of bias (*i.e., unclear selective reporting due to irretrievable protocol*).
- *GFO at Month 3:* The odds of improved global function is 352% higher in the cerebrolysin group compared to neuro-rehabilitation alone (*OR: 4.52; 95% CI 2.72 to 8.23*) based on the results of one RCT (Muresanu et al, 2016) as adopted from Beghi et al (2021). The overall certainty of evidence was ***low***, with serious risk of imprecision (*wide CI*) and serious risk of bias (*i.e., unclear missing outcomes and selective reporting due to irretrievable protocol*).

Table 7. Efficacy results per outcome

Author, Year, SD	*Efficacy Outcome/s*	*Results*		*Interpretation*
		Intervention	*Comparator*	
Beghi et al (2021)	Early Motor Performance at Month 1 (k = 1)	Cerebrolysin + SOC and/or neurorehabilitation N = 102^^^	SOC and/or neurorehabilitation N = 101^^^	Based on one RCT, the odds of improved early motor performance at month 1 after stroke is 135% higher in the cerebrolysin group when compared with neurorehabilitation alone. (*low certainty of evidence*)
		OR: 2.35; 95% CI: 1.43 to 4.04; I^2 = N/A		
	Early Motor Performance at Month 3 (k = 2)	Cerebrolysin + SOC and/or neurorehabilitation N=221^^^	SOC and/or neurorehabilitation N=221^^^	**Not statistically significant** (*inconclusive; very low certainty of evidence*)
		Pooled OR: 2.12; 95% CI: 0.68 to 6.59; **I^2 = 89.40%**		
	Neurological Function at Month 1 (k = 4)	Cerebrolysin + SOC and/or neurorehabilitation N=273^^^	SOC and/or neurorehabilitation N=271^^^	Based on four RCTs, the odds of improved neurological function at month 1 after stroke is 94% higher in the cerebrolysin group when compared with neurorehabilitation alone. *(low certainty of evidence)*
		Pooled OR: 1.94; 95% CI: 1.35 to 2.77; I^2 = 18.08%		
	Neurological Function at Month 3 (k = 2)	Cerebrolysin + SOC and/or neurorehabilitation N=126^^^	SOC and/or neurorehabilitation N=122^^^	Based on two RCTs, the odds of improved neurological function is 267% higher in the cerebrolysin group when compared with neurorehabilitation alone. *(low certainty of evidence)*
		Pooled OR: 3.67; 95% CI: 1.89 to 7.13; I^2 = 28.72%		
	Global Functional Outcome at Month 1 (k = 1)	Cerebrolysin + SOC and/or neurorehabilitation N=30^^^	SOC and/or neurorehabilitation N=29^^^	Based on one number of RCTs, the odds of improved global function is 352% higher in the cerebrolysin group when compared with neurorehabilitation alone. *(low certainty of evidence)*
		OR: 4.52; 95% CI 1.88 to 14.93; I^2 = N/A		
	Global Functional Outcome at Month 3 (k = 1)	Cerebrolysin + SOC and/or neurorehabilitation N=30^^^	SOC and/or neurorehabilitation N=29^^^	Based on one RCT, at month 3 after stroke, the odds of improved global function is 352% higher in the cerebrolysin group compared to neurorehabilitation alone. *(low quality evidence)*
		OR: 4.52; 95% CI 2.72 to 8.23; I^2 = N/A		

^^^Number of events cannot be retrieved. Presentation in the forest plots includes only the N of I / N of C

Results on Safety

*NOTE: RCTs in red font have **inaccessible full-text articles.***

Out of the three included SRs, the most recent results from Strilciuc et al (2021) were adopted for four safety outcomes (*i.e., any adverse event, all-cause death, severe adverse events [SAEs], non-fatal SAEs*). Only the results of fatal SAEs, an outcome uniquely reported by only one SR, was adopted from Ziganshina et al (2020). All outcome results were pooled by their respective SRs and were adopted in our assessment.

Among the five safety outcomes, only *any AEs* provided an equivalent relative effect between cerebrolysin + SOC and/or rehabilitation and SOC and/or rehabilitation alone, based on low certainty of evidence. As for the remaining four outcomes (*i.e., all-cause death, SAEs, non-fatal SAEs, fatal SAEs*), all outcomes yielded inconclusive results (*based on very low certainty of evidence for three outcomes; low certainty of evidence for one outcome; moderate certainty of evidence for one outcome*).

Safety Outcome 1: Any Adverse Event (AE)

Based on the results of 11 RCTs (Ladurner et al, 2005; Skvortsova et al, 2004; Shamalov et al, 2010; Gharagozli et al, 2017; Heiss et al, 2012; Lang et al, 2013; Muresanu et al, 2016; Guekht et al, 2015, Chang et al, 2016; Xue et al, 2016; Stan et al, 2017), as pooled by the most recent SR (Strilciuc et al, 2021), the risk of any adverse event was comparable between the cerebrolysin and placebo arms (*RR 0.98, 95% CI 0.88 to 1.09; I^2=30.0%,*). The overall certainty of evidence was ***low***, with serious risk of bias (*i.e.,unclear ROB due to allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors*) and serious risk of imprecision.

Safety Outcome 2: All-cause death

Based on the results of 12 RCTs (Ladurner et al, 2005; Skvortsova et al, 2004; Shamalov et al, 2010; Gharagozli et al, 2017; Heiss et al, 2012; Lang et al, 2013; Amiri-Nikipour et al, 2014; Muresanu et al, 2016; Guekht et al, 2015, Chang et al, 2016; Xue et al, 2016; Stan et al, 2017), as pooled by the most recent SR Strilciuc et al (2021), the risk of death from all causes was not statistically significant (*i.e., inconclusive*) in the cerebrolysin group when compared with the placebo group (*RR: 0.83, 95% CI 0.57 to 1.23; I^2=0.0%*). The overall certainty of evidence was ***very low***, with serious risk of bias (*i.e., unclear ROB due to random sequence generation, allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors*) and very serious risk of imprecision.

Safety Outcome 3: Severe Adverse Events (SAEs)

Based on the results of 11 RCTs (Ladurner et al, 2005; Skvortsova et al, 2004; Shamalov et al, 2010; Gharagozli et al, 2017; Heiss et al, 2012; Lang et al, 2013; Muresanu et al, 2016; Guekht et al, 2015, Chang et al, 2016; Xue et al, 2016; Stan et al, 2017) as pooled by the most recent SR Strilciuc et al (2021), the risk of serious adverse events was not statistically significant (*i.e., inconclusive*) in the cerebrolysin group when compared with the placebo group (*RR: 0.99, 95% CI: 0.74 to 1.32; I^2=0.0%*). The overall certainty of evidence was ***very low***, with serious risk of bias (*i.e., unclear ROB due to allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors*) and very serious risk of imprecision.

Safety Outcome 3.1: Non-fatal SAEs

Based on the results of 11 RCTs (Ladurner et al, 2005; Skvortsova et al, 2004; Shamalov et al, 2010; Gharagozli et al, 2017; Heiss et al, 2012; Lang et al, 2013; Muresanu et al, 2016; Guekht et al, 2015, Chang et al, 2016; Xue et al, 2016; Stan et al, 2017), as pooled by the most recent SR (Strilciuc et al, 2021), the risk for non-fatal SAEs was not statistically significant (*i.e. inconclusive*) in the cerebrolysin group when compared with the placebo group (*RR: 1.18, 95% CI 0.75 to 1.86; I^2=0.0%*). The overall certainty of evidence was ***very low***, with serious risk of bias (*i.e., unclear ROB due to allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors*) and very serious risk of imprecision.

Safety Outcome 3.2: Fatal SAEs

Only Ziganshina et al (2020) pooled the results of fatal SAEs based on 3 RCTs (Heiss et al, 2012; Lang et al, 2013; Ladurner et al, 2005). According to the review, the pooled risk is not statistically significant (*i.e. inconclusive*) in the cerebrolysin arm when compared with the placebo arm (*RR: 0.90, 95% CI 0.59 to 1.38; I^2=0.0%*). The overall certainty of evidence was ***moderate***, with serious risk of bias (*i.e., highest ROB among included studies is unclear*).

Table 8. Safety results per outcome

Author, Year, SD	*Safety Outcome/s*	*Results*		*Interpretation*
		Intervention	*Comparator*	
Strilciuc et al (2021)	Any AE (k = 11)	Cerebrolysin + SOC and/or rehabilitation n/N = 472/1078 (43.78%)	Placebo + SOC n/N = 470/1078 (43.60%)	**Not statistically significant** (*equivalent; low certainty of evidence*)
		Pooled RR 0.98, 95% CI 0.88 to 1.09; I^2=30.0%,		
	All-Cause Death (k = 12)	Cerebrolysin + SOC n/N = 45/1101 (4.09%)	Placebo + SOC n/N = 55/1101 (4.99%)	**Not statistically significant** (*inconclusive; very low certainty of evidence*)
		Pooled RR: 0.83, 95% CI 0.57 to 1.23; I^2=0.0%		
	SAE (k = 11)	Cerebrolysin + SOC n/N = 85/1078 (7.88%)	Placebo + SOC n/N = 85/1076 (7.89%)	**Not statistically significant** (*inconclusive; very low certainty of evidence*)
		Pooled RR: 0.99, 95% CI: 0.74 to 1.32; I^2 0.0%		
	Non-Fatal SAE (k = 11)	Cerebrolysin + SOC n/N = 41/1078 (3.80%)	Placebo + SOC n/N = 32/1078 (2.97%)	**Not statistically significant** (*inconclusive; very low certainty of evidence*)
		Pooled RR: 1.18, 95% CI 0.75 to 1.86; I^2=0.0%		
Ziganshina et al (2020)	Fatal SAE (k = 3)	Cerebrolysin n/N = 38/667 (5.70%)	Placebo n/N = 42/668 (6.29%)	**Not statistically significant** (*inconclusive; moderate certainty of evidence*)
		Pooled RR: 0.90, 95% CI 0.59 to 1.38; I^2=0.0%		

Review of Clinical Practice Guidelines on Cerebrolysin

CPGs scoped by the HTA Division for the review of recommendations totaled 18, but only seven CPGs from different societies mentioned cerebrolysin (*i.e., European Academy of Neurology [EAN]; European Federation of Neurorehabilitation Sciences [EFNR]; European Stroke Organization [ESO]; World Federation for Neurorehabilitation [WFNR]; Canadian Partnership for Stroke Recovery [CPSR]; American Heart Association [AHA]; Stroke Society of the Philippines [SSP]*). No WHO EML review was found for cerebrolysin.

- There were six international CPGs (i.e., *EAN/EFNR (2021)*, *ESO/EAN (2021)*, *WFNR (2021)*, *AHA*), while only one CPG was published locally (*i.e., SSP Handbook of Stroke*).
- Two CPGs (*i.e., EAN/EFNR, CPSR*) had **positive recommendations.**
  - **[EU]** EAN/EFNR (2021): A weak recommendation for cerebrolysin (30 ml, intravenous, minimum 10 days) is given for early motor neurorehabilitation after moderate–severe ischaemic stroke, based on low and high quality of evidence across primary and secondary critical outcomes.
  - **[Canada]** CPSR (2020): Cerebrolysin may improve upper limb motor function, dexterity, and measures of independence/daily living, based on Category 1A to 1B level of evidence.
  - **[Austria / Translated from German]** Austrian Stroke Society (2018)**:** There is positive evidence of the effectiveness of a peptide preparation in rehabilitation: Cerebrolysin (30 ml for 3 weeks or longer) (***class 2, level B***) is able to improve rehabilitation, especially of the upper extremities after a stroke.
- Three CPGs (*i.e., ESO/EAN AHA*) gave **negative recommendations.**
  - **[UK]** ESO/EAN (2021): The available evidence suggests that any cognitive benefits of cerebrolysin are likely to be modest and there is risk of serious adverse events with treatment. Considering the balance of risks and harms, we suggest against using these agents for post-stroke cognitive impairment (PSCI), based on very low quality of evidence.
  - **[US]** AHA (2019): The guideline does not recommend the administration of any medicative and non-medicative agents with an assumed neuroprotective activity in the acute phase of ischemic stroke, based on Class III-A level of evidence.
  - **[US]** AHA (2019): At present, pharmacological or nonpharmacological treatments with putative neuroprotective actions are not recommended.
- Two CPGs (*i.e., SSP, WFNR*) explained that the use of cerebrolysin is **at the discretion of the attending physician.**
  - **[Philippines]** SSP (2014)**:**
    - Clinical trials involving more than 1,500 patients since 1994 has shown favorable results on motor function, activities of daily living, cognitive performance, and faster recovery with use of Cerebrolysin.
    - The Cerebrolysin in Patients with Acute Ischemic Stroke in Asia (CASTA) trial has shown no overall difference in outcomes between those who received Cerebrolysin and those in the placebo group at 90 days.
    - A favorable trend towards benefit was seen in the more severely affected patients in post hoc analysis.
    - The use of drugs with neurorestorative and neuroprotective properties (*i.e., **cerebrolysin**, citicoline, NeuroAID*) in acute stroke remains a matter of preference of the attending physician.
  - **[Global]** WFNR (2020):
    - Medication thought to modify neuroplasticity and motor recovery post-stroke has not been investigated extensively.

- Any data regarding arm rehabilitation is regarded as preliminary (*e.g. for l-dopa, donepezil, d-amphetamine, fluoxetine, or* ***cerebrolysin***) and not yet sufficient to recommend its routine clinical use.
- Individualized treatment decisions (e.g. for l-dopa, fluoxetine, or ***cerebrolysin***) *are at the discretion of the physician in charge*, mostly as "off-label" treatment.

Cost-Effectiveness

The HTAC judgment on the clinical efficacy, effectiveness and safety is that cerebrolysin is non-inferior in its use among adults post-stroke compared to rehabilitation or standard of care alone . As such, a cost-minimization analysis or a comparative costing analysis, instead of cost-effectiveness analysis or cost-utility analysis was performed, following the HTAC methods. This will be discussed in the next section under Affordability and Viability.

Affordability and viability

For the costing analysis, the direct medical cost items included were the: (1) government procurement price of cerebrolysin for the cost of drug regimen provided by the sole local distributor, (2) cost of rehabilitation obtained from the lowest and most recent price scoped from various government hospitals, and (3) cost of other direct medical cost items (*i.e., IV cannula, IV infusion set, saline solution*) also scoped from the lowest and most updated price of various government hospitals, from a third-party payer's / government's perspective. From these, the final costing outputs were the total cost of treatment regimen per patient and for all expected users. Regimens and resource utilization were consulted with SSP. Cerebrolysin is given for 21 days throughout the whole treatment course. For purposes of this costing analysis, we calculated the cost for one (1) year of treatment. The frequency of rehabilitation, on the other hand, differed between the two groups (*i.e., 1 session per day for 21 days for the intervention group; 5 times a week for 6 months for the comparator group*), as mentioned by SSP.

Comparative Costing per Regimen per User and for All Users

The total cost of treatment for post-ischemic stroke (*i.e., drug regimen and other associated cost of administration*) per target user per year is **₱45,317.25** for *cerebrolysin + rehabilitation* and **₱20,250.00** for *rehabilitation alone*. The incremental cost per target user per year was estimated to be **₱25,067.25**.

The expected number of users for 2023 is estimated to be *67,239*. The target users for both the intervention and comparator arms were assumed to be the number of ***new cases*** of post-ischemic stroke each year. This was considered because cerebrolysin and rehabilitation were used for less than one year (*i.e., for the intervention, cerebrolysin + rehabilitation is given for 21 days only; for the comparator, rehabilitation is given for five times a week for 6 months only*). It is assumed that the treatments received by the target users will not be carried over to the next year. The incidence rate was adopted from the age-standardized rates from the Global Burden of Disease study (GBD, 2019) (*i.e., 96.8 per 100,000 individuals for* ***incidence***).

From this, the total costs for one year of treatment are as follows: **₱3.05 B** for *cerebrolysin + rehabilitation* and **₱1.36 B** for *rehabilitation alone*. The incremental cost of using *cerebrolysin + rehabilitation* over *rehabilitation alone* is estimated to be at **₱1.69 B.** The projection of total cost from 2023 to 2025 is detailed in the Budget Impact Analysis.

Table 9: Costing Analysis

Parameter	Intervention *Cerebrolysin + Rehabilitation*	Comparator *Rehabilitation*	Remarks Reference/s, Year
Part 1: Cost of Drug Regimen			
Cost of Cerebrolysin			
Unit cost of cerebrolysin (*A*)	₱646.00		Globo Asiatico, 2023
Treatment Regimen	30 mL OD x 21 days		PNF Form
No. of amps per treatment (*B*)	3		30 mL/day / 10 mL/amp = 3 vials per day
Duration of treatment course in days	21		
Cost of cerebrolysin per user (*D = A x B x C*)	**₱40,698.00**		
Cost of Rehabilitation			
Unit cost of Rehab (*E*)	₱150.00	₱150.00	*Corazon Montelibano Hospital (2021)*
Treatment Regimen	1 session per day x 21 days	1 hour, 5 times a week x 27 weeks	SSP DEF I: Stroke Rehabilitation Clinician Handbook (2020) C: Philippine Association of Rehabilitation Medicine (2017)
Frequency of rehab sessions (*F*)	1 per day	5 per week	
Duration of treatment (*G*)	21 days	6 months (27 weeks)	
Cost of rehabilitation per user (*H = E x F x G*)	**₱3,150.00**	**₱20,250.00**	
Cost of Intervention / Comparator per Patient per Treatment Course			
Total Cost (*I = D + H*)	**₱43,848.00**	**₱20,250.00**	
Part 2: Other costs (e.g., cost of monitoring, cost of AE management)			
Cost of Consumables			
Consumables changed every 7 days			
Unit cost of IV catheter (*J*)	₱60.00		Corazon Montelibano Hospital (2023) Gauge 18 used by SSP
Unit cost of IV infusion (*K*)	₱36.00		
Number of units needed (*L*)	3		Assumption: Consumables are changed every 7 days
Sub-Total (*M = [J+K] x L*)	₱288.00		
Consumables changed daily			
Unit cost of saline solution (*N*)	₱56.25		Corazon Montelibano Hospital (2023)
Number of units needed (*O*)	1		70 ml needed Wastage (ml) = 100 mL/bottle - 70 mL = 30 mL *Assumption: The IV bottle cannot be reused once opened.*
Sub-Total (*P = N x O*)	21		SSP DEF
Total Associated Medical Costs			
Total Cost (*Q = M + P*)	**₱1,469.25**		
Part 3: Total Cost of Treatment Regimen per patient			
Cost of Regimen per User (*R = I + Q*)	**₱45,317.25**	**₱20,250.00**	
Incremental cost of treatment (*R of intervention - R of comparator*)	**₱25,067.25**		
Part 4: Total Cost of Treatment Regimen for all users per year			
Expected no. of target users (*S*)	67,239		HTAD Scoping (GBD 2019 Incidence: 96.8 per 100,000)
Cost of Regimen for all users (*T = R x S*)	**₱3,047,086,572.75**	**₱1,361,589,750.00**	
in billions	**₱3.05 B**	**₱1.36 B**	
Incremental cost of treatment (*T of intervention - T of comparator*)	**₱1.69 B**		

Budget Impact Analysis

The budget impact analysis over a three-year horizon for cerebrolysin in combination with rehabilitation compared to rehabilitation was performed using data from sources indicated in Annex A.. For 2023-2025, the cost per target user was multiplied with the number of ***new cases*** of post-ischemic stroke.

The total number of users per year is estimated to be as follows: *67,239* for 2023; *68,469* for 2024; and *69,674* for 2025. Calculation of users was the same as with the computation of the expected number of users in the costing analysis. The estimated total cost of treatment with cerebrolysin in combination with rehabilitation and rehabilitation alone for 3 years is **₱9.31 B** and **₱4.16 B** respectively, incurring an additional cost of **₱5.15 B**. In general, the intervention ***will entail higher costs*** than the comparator.

Table 10. Projection of expected users from 2019-2025

Year	Total ADULT Population (POPCEN 2015)	Incidence Rate	Number of New Cases per Year
2019	64,126,879		
2020	65,478,942	0.0010	63,436
2021	66,807,748	0.0010	64,723
2022	68,116,324	0.0010	65,991
2023	**69,403,992**	**0.0010**	**67,239**
2024	**70,673,575**	**0.0010**	**68,469**
2025	**71,917,333**	**0.0010**	**69,674**

Table 11: Three-Year Budget Impact Analysis

Year	**Total No. of Users per year**	**INTERVENTION** *Cerebrolysin + Rehabilitation*	**COMPARATOR** *Rehabilitation Alone*	**INCREMENTAL COST**
Year 1 (2023)	67,239	₱3.05 B	₱1.36 B	₱1.69 B
Year 2 (2024)	68,469	₱3.10 B	₱1.39 B	₱1.72 B
Year 3 (2025)	69,674	₱3.16 B	₱1.41 B	₱1.75 B
TOTAL (*in billions*)		₱9.31 B	₱4.16 B	**₱ 5.15 B**

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Annex A. GRADE Tables

GRADE of Efficacy Outcomes

Certainty assessment							№ of patients		Relative Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerebrolysin + rehab	Rehab alone			
Early motor performance month 1											
1	RCT	serious[a,b]	not assessed	not serious	serious[e]	none	-/102	-/101	**OR 2.35** (1.43 to 4.04)	⊕⊕◯◯ Low	**Critical**
Early motor performance month 3											
2	RCT	serious[a,b]	very serious (I^2=89.40%)	not serious	very serious[d,e]	none	-/221	-/221	**OR 2.12** (0.68 to 6.59)	⊕◯◯◯ Very low	**Critical**
Neurological function month 1											
4	RCT	serious[a,c]	not serious (I^2=18.08%)	not serious	serious[e]	none	-/273	-/271	**OR 1.94** (1.35 to 2.77)	⊕⊕◯◯ Low	**Critical**
Neurological function month 3											
2	RCT	serious[a,b,c]	not serious (I^2=28.72%)	not serious	serious[e]	none	-/126	-/122	**OR 3.67** (1.89 to 7.13)	⊕⊕◯◯ Low	**Critical**
Global functional outcome month 1											
1	RCT	serious[b]	not assessed	not serious	serious[e]	none	-/104	-/101	**OR 4.52** (1.88 to 14.93)	⊕⊕◯◯ Low	**Critical**
Global functional outcome month 3											
1	RCT	serious[a,b]	not assessed	not serious	serious[e]	none	-/30	-/29	**OR 4.52** (2.72 to 8.23)	⊕⊕◯◯ Low	**Critical**

CI: confidence interval; n events not reported in studies

a. Unclear overall rating: Unclear missing outcomes due to irretrievable protocol (Amiri-Nikipour et al., 2014; Muresanu et al., 2016; Guekht et al., 2015; Shamalov et al., 2010, Stan et al., 2017)
b. Unclear overall rating: Unclear selective reporting domains due to irretrievable protocol (Amiri-Nikipour et al., 2014; Muresanu et al., 2016; Guekht et al., 2015; Shamalov et al., 2010)
c. Unclear overall rating: Unclear allocation concealment (Amiri-Nikipour et al., 2014)
d. Crossing the null
e. Wide CI.

GRADE of Safety Outcomes **(ROB adopted from Strilciuc et al [2021]):**

Certainty assessment							№ of patients		Relative Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerebrolysin + rehab/SOC	Placebo + rehab/SOC			
Severe adverse events											
11	RCT	serious[a,c]	not serious (I^2=0.0%)	not serious	very serious[d,e]	none	85/1078 (7.9%)	85/1076 (7.9%)	**RR 0.99** (0.74 to 1.32)	⊕◯◯◯ Very low	**Critical**
Any adverse events											
11	RCT	serious[a,c]	not serious (I^2=30.0%)	not serious	serious[d]	none	472/1078 (43.8%)	470/1078 (43.6%)	**RR 0.98** (0.88 to 1.09)	⊕⊕◯◯ Low	**Critical**
Non-fatal adverse events											
11	RCT	serious[a,c]	not serious (I^2=0.0%)	not serious	very serious[d,e]	none	41/1078 (3.8%)	32/1078 (3.0%)	**RR 1.18** (0.75 to 1.86)	⊕◯◯◯ Very low	**Critical**
All-cause Death											
12	RCT	serious[a,b,c]	not serious (I^2=0.0%)	not serious	very serious[d,e]	none	45/1101 (4.1%)	55/1101 (5.0%)	**RR 0.83** (0.57 to 1.23)	⊕◯◯◯ Very low	**Critical**

CI: confidence interval; **RR:** risk ratio; a. Based on highest ROB from individual studies; b. Wide CI, crossing the null; c. Narrow CI, crossing the null
a. Unclear ROB (Gharagozli et al, 2017) for the following domains: allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors
b. Unclear ROB (Amiri-Niikpour, 2014) for the following domains: generation sequence, allocation concealment, blinding of participants and healthcare providers, blinding of outcome assessors
c. Unclear ROB: (Xue et al., 2016): for the following domains: blinding of participants and healthcare providers, blinding of outcome assessors
d. Crosses the null
e. Wide CI

Safety Outcome **(GRADE adopted from Ziganshina et al [2020])**

Certainty assessment							№ of patients		Relative Effect (95% CI)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cerebrolysin + SOC	Placebo + SOC			
Fatal serious adverse events											
3	RCT						63 per 1000	57 per 1000 (37 to 87)	**RR 0.90** (0.59 to 1.38)	⊕⊕⊕⊖ Moderate[a,b,c]	**Critical**

a. Downgraded by one level for risk of bias because most information came from studies at low or unclear risk of bias.
b. No serious inconsistency. Three eligible multicentre studies contributed to the outcome total number of people with fatal SAEs; the newly included Gharagozli 2017 study contributed to the outcomes total number of people with SAEs and total number of people with non-fatal SAEs. detected no statistical heterogeneity for any of these outcomes.
c. No serious indirectness. The studies, three of which were multicentre, were conducted in seven EU countries: Austria, Croatia, the Czech Republic, Hungary, Russia, Slovakia, Slovenia; and five Asian countries: China, Hong Kong, Iran, Myanmar, South Korea. The results can be generalised to other populations and situations between 2003 and 2014.

Annex B. HTAD-assessed ROB of studies included

Beghi et al (2021)

+	LOW	-	HIGH	?	UNCLEAR

Study (First Author, Year)	Randomization	Allocation Concealment	Blinding (Participants)	Blinding (Investigators)	Blinding (Assessors)	Missing Outcomes / Follow-Up	Selective Reporting	Overall Rob
Amiri-Nikipour et al (2014)	+	?	+	+	+	?	?	?
Muresanu et al (2016)	+	+	+	+	+	?	?	?
Guekht et al (2015)	+	+	+	+	+	?	?	?
Shamalov et al (2010)	+	+	+	+	+	?	?	?
Stan et al, 2017	+	+	+	+	+	?	+	?

Strilciuc et al. (2021)

Bias[1]	Selection		Performance	Detection	Attrition	Reporting	Other
Study	Appropriate generation of the allocation sequence	Conceal-ment of the allocation sequence	Blinding of participant and health care providers	Blinding of outcome assessors	Assessment of incomplete outcome data	Selective outcome reporting	Other biases
Ladurner 2005 [21]	Low risk	Low risk[1]	Low risk	Low risk	Low risk[2]	Low risk[3]	Low risk[3]
Skvortsova 2004 [22]	Low risk[4]	Low risk[4]	Low risk[4]	Low risk[4]	Low risk[5]	Low risk[6]	Low risk[6]
Shamalov 2010 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gharagozli 2017 [17]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk[7]	Low risk	Low risk[7]
Heiss 2012 [18]	Low risk[8]	Low risk	Low risk	Low risk	Low risk[9]	Low risk[10]	Low risk[11]
Lang 2013 [19]	Low risk[12]	Low risk[12]	Low risk	Low risk	Low risk[13]	Low risk[14]	Low risk
Amiri-Nikpour 2014 [24]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Muresanu 2016 [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Guekht 2015 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chang 2016 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xue 2016 [26]	Low risk[15]	Low risk[15]	Unclear risk	Unclear risk	Low risk[16]	Low risk[16]	Low risk[16]
Stan 2017 [10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Risk of bias assessment for the safety evaluations was performed using all available data from original publications. In unclear cases, supplementary study documents were requested from the original authors (such as Study Protocols, Clinical Study Reports, etc.). Inclusion of any supplements is documented in the footnotes of this table.

Annex C. AMSTAR Appraisal of Studies

Domain	Beghi et al (2021)		Strilciuc et al (2021)		Ziganshina et al (2020)	
	Result	Remarks / Page where justification can be found	Result	Remarks / Page where justification can be found	Result	Remarks / Page where justification can be found
1	Y	p. 2832	Y	p. 2	Y	p. 11 -12
2*	Y	See *study protocol* and *analysis plan* Main write-up: p. 2832	Y	pp. 2-4	Y	p. 80 *Link to Protocol*
3	N	Included NRSI but without explanation.	N	While the study mentioned in p. 8 the reason for including the ***max no.*** *of RCTs*, they did not explain why RCTs only.	Y	*Link to Protocol*
4*	PY	See appendix S3; no explicit mention of searching reference list	Y	pp. 2-3	Y	p. 12, 23
5	Y	pp. 2833	Y	p. 3	Y	p. 13
6	Y	pp. 2833-2834	Y	p. 3	Y	p. 13
7*	Y	See *supplementary 6*	PY	Contains description of the studies excluded but no explicitly mentioned reason for excluding such studies	Y	pp. 56-60
8	PY	See *supplementary 6; no doses mentioned*	Y	pp. 5-6	Y	pp. 34-56
9*	Y	See *supplementary 6*	Y	pp. 3-4; see also *supplementary 1*	Y	pp. 36-56
10	N	No mention in the SR of funding source for	N	No mention in the SR of funding source for	Y	pp. 35-56

		studies included in the review.		studies included in the review.		
11*	**N**	See *supplementary 7*; *supplementary 9*	**Y**	pp. 3-4, 9-11	**Y**	p. 13
12	**Y**	See *supplementary 6*; *supplementary 10*	**Y**	p. 4; see also *supplementary 1*	**Y**	p. 14
13*	**Y**	pp. 2836	**Y**	p. 4; see also *supplementary 1*	**Y**	p. 24
14	**N**	No explanation of heterogeneity causes	**Y**	p. 9	**Y**	p. 20
15*	**N**	No mention of publication bias examination	**Y**	p. 3	**Y**	p. 13
16	**Y**	Investigators with COI has abstained from voting on evidence for cerebrolysin in this guideline.	**Y**	p. 10	**Y**	p. 80
Overall Rating:		**CRITICALLY LOW**		**MODERATE QUALITY**		**HIGH QUALITY**

Annex D. PICO of the trials in the included Systematic Reviews

*NOTE: RCTs in red font have **inaccessible full-text articles.***

Study	Population	Intervention	Comparator	Outcome	SD
CEREBROLYSIN AND RECOVERY AFTER STROKE [CARS] TRIAL					
Muresanu et al (2016) *[CARS 1]*	Adults with moderate to severe ischemic supratentorial strokes	Cerebrolysin + rehabilitation *n=104/208*	Placebo (saline) + rehabilitation *n=104/208*	**Efficacy:** • Global status change (Measured with ARAT, NIHSS, mRS, BI) **Safety:** • SAEs, TEAEs	Phase II RCT prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group
Guekht et al (2015) in Guekht et al (2017) *Full-text inaccessible [CARS 2]*	Two identical stroke studies (CARS-1 and CARS-2)	Cerebrolysin + rehabilitation *n=120/240*	Placebo (unspecified)+ rehabilitation *n=120/240*	**Efficacy:** • Neurological impairment (measured with ARAT) • Gait velocity • Fine motor function • Global neurological status • Quality of life **Safety:** • AEs, SAEs	Randomized, placebo-controlled, double-blind, multicenter
CEREBROLYSIN ACUTE STROKE TREATMENT IN ASIA [CASTA] TRIAL					
Heiss et al (2012) [CASTA]	Acute ischemic hemispheric stroke	Cerebrolysin + aspirin *n=529/1070*	Placebo (saline) + aspirin *n=541/1070*	**Efficacy:** • Severity of neurological deficit (measured with NIHSS, mRS, BI) • Mortality in subgroup NIHSS>12 • Quality of life (measured with SF-12) **Safety:** • AEs, SAEs, fatal AEs, death	Phase IV double-blinded, placebo-controlled
COMBINED TREATMENT WITH ALTEPLASE (RT-PA) AND CEREBROLYSIN IN ACUTE ISCHEMIC HEMISPHERIC STROKE (CERE-LYSE-1)					
Lang et al (2013) *[CERE-LYSE-1]*	Acute ischemic hemispheric stroke	Cerebrolysin + alteplase	Placebo (saline) +	**Efficacy:** • Neurological function (measured with NIHSS, BI, Glasgow	Phase III RCT prospective,

		n=60/119	alteplase *n=59/119*	Outcome Score) **Safety:** • AEs, SAEs, Death	randomized, placebo-controlled, double-blinded
EFFECTS OF CEREBROLYSIN ON MOTOR RECOVERY IN PATIENTS WITH SUBACUTE STROKE [E-COMPASS]					
Chang et al (2016) *[E-COMPASS]*	Acute focal ischemic stroke within the first 7 days after stroke	Cerebrolysin + rehabilitation *n=35/70*	Placebo (saline) + rehabilitation *n=35/70*	**Efficacy** • Stroke severity (measured with NIHSS) • Motor function (measured with Fugl-Meyer assessment) • Motor network plasticity (measured with diffusion tensor imaging **Safety** • AEs, SAEs	Phase IV prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group
OTHER TRIALS					
Amiri-Nikipour et al (2014)	Acute focal ischemic stroke undergoing rehabilitation therapy	Cerebrolysin + aspirin *n=23/46*	Placebo (saline) + aspirin *n=23/46*	**Efficacy:** • Neurological outcomes (change in NIHSS score) • Pulsatility index (to evaluate cerebral blood flow)	Randomized, double-blinded, placebo-controlled
Gharagozli et al (2017)	Individuals within 18 hours after the onset of stroke	Cerebrolysin + SOC (aspirin, pentoxifylline or low-dose heparin) *n=50/100*	Placebo (saline) + SOC (aspirin, pentoxifylline or low-dose heparin) *n=50/100*	**Efficacy:** • Improvement in neurological outcomes (measured with NIHSS, mRS, Clinical Global Impression [CGI], Patient Global Satisfaction [PGS], Mini Mental State Examination [MMSE]) **Safety** • AEs, SAEs, All-cause death	Prospective, randomized, double-blinded, placebo-controlled, multicenter, parallel-group
Ladurner et al (2005)	First acute ischaemic stroke with clinical symptoms of middle cerebral artery area	Cerebrolysin + aspirin + pentoxifylline *n=78/146*	Placebo (saline) + aspirin + pentoxifylline *n=68/146*	**Efficacy:** • Change in neurological, functional, and cognitive performance (measured with Canadian Neurological Scale [CNS], BI, Glasgow Coma Scale [GCS], MMSE, Syndrome Short Test [SST], Self-Assessment Scale [SAS], Hamilton Rating Scale for Depression [HAMD]) **Safety:** • AEs, SAEs, Death	Randomized, placebo-controlled, parallel group
Shamalov et al	Adults with acute	Cerebrolysin	Placebo	**Efficacy:**	Prospective, randomized,

(2010) *Full-text translated only*	ischemic stroke	*n/N = 24/47*	(saline) *n = 23/47*	• Decrease in stroke volume	double-blinded, placebo-controlled, multicenter, parallel-group
Skvortsova et al (2004) *Full-text inaccessible*	Adults with ischemic stroke in carotid artery	Cerebrolysin + aspirin, pentoxifylline, hemodilution and heparin (*when needed*) *n=12/36*	Placebo (saline) + aspirin, pentoxifylline, hemodilution and heparin (*when needed*) *n=12/36*	**Efficacy** • Reduction in volume of MRI ischemic focus	Randomized, double-blind, placebo-controlled
Stan et al (2017)	Adults with ischemic supratentorial strokes	Cerebrolysin + rehabilitation *n=30/60*	Placebo (saline) + rehabilitation *n=30/60*	**Efficacy:** • Neurological function (Measured with NIHSS from baseline to day 30) • Global functional outcome (Measured with mRS and BI from baseline to day 30) **Safety:** • SAEs	Prospective, randomized, double-blind, placebo-controlled clinical study
Xue et al (2016)	Acute ischemic stroke	Cerebrolysin + SOC*** *n= 20/60*	DL-3-n-butylphthalide + SOC*** *n=20/60* Placebo *n=20/60*	**Efficacy:** • Neurological and behavioral outcomes (measured with NIHSS, Barthel Index) **Safety:** • AEs	Phase II RCT randomized, double-blind

****Antithrombotic drugs, hypoglycemic agents, antilipemic agents, antihypertensive(s) and dehydration*

Annex E. CPG Recommendations for Cerebrolysin in Patients with Acute Ischemic Stroke

Guideline *(Country, Year of publication)*	**P**	**I**	**Indication and Recommendation**
With Positive Recommendations			
EAN/EFNR (2021) *European Academy of Neurology / European Federation of Neurorehabilitation Sciences*	Early motor rehabilitation after acute ischemic stroke	Pharmacological treatment *(i.e., cerebrolysin)*	Based on low and high quality of evidence across primary and secondary critical outcomes, ***a weak recommendation for cerebrolysin*** (30 ml, intravenous, minimum 10 days) is given for early motor neurorehabilitation after moderate–severe ischaemic stroke. Weak Recommendation: ● **For Patients:** Most people in your situation would want the recommended course of action, but many would not. ● **For Healthcare Providers:** You should organize that different choices will be appropriate for different patients. You must help each patient to arrive at a management decision with her/his values and preferences. ● **For Policy:** Policy-making will require substantial debate and involvement of many stakeholders.
CPSR (2020) *Canadian Partnership for Stroke Recovery*	Acute ischemic stroke	Neuropeptides *(i.e., cerebrolysin)*	***Cerebrolysin may improve*** upper limb motor function, dexterity, and measures of independence/daily living. Level of Evidence ● **Motor Function:** ○ Category 1A ○ *More than one higher RCT: Randomized Controlled Trial, PEDro score ≥ 6. Includes within subjects comparison with randomized conditions and cross- over designs.* ● **ADLs:** ○ Category 1B

			○ *1 higher RCT; PEDro*** score ≥ 6* ● **Stroke Severity:** ○ Category 1B ○ *1 higher RCT; PEDro*** score ≥ 6* ****Methodological quality of individual RCTs was assessed using the Physiotherapy Evidence Database (PEDro) tool. PEDro (which can be found at: http://www.pedro.fhs.usyd.edu.au/scale_item.html) was developed for the purpose of accessing bibliographic details and abstracts of randomized-controlled trials (RCT), quasi-randomized studies and systematic reviews in physiotherapy*
Austrian Stroke Society (2018)	Post-Stroke	Cerebrolysin	**[Translated from German]** There is positive evidence of the effectiveness of a peptide preparation in rehabilitation: Cerebrolysin (***Class II, Level B***) is able to improve rehabilitation, especially of the upper extremities after a stroke. Level of Evidence: **Class II:** Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e or a randomized, controlled trial in a representative population that lacks one criteria a–e. a) Randomization concealment b) Primary outcome(s) is/are clearly defined c) Exclusion/inclusion criteria are clearly defined d) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and e) Relevant baseline characteristics are presented & substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. **Level B:** Established as probably effective, ineffective or harmful for a therapeutic intervention, and requires at least one convincing Class II study or overwhelming Class III evidence. ● *For reference of **Class III** evidence in the definition of Level B:* ○ *All other controlled trials in a representative population, where outcome assessment is independent of patient treatment.* ○ *Trials include well-defined natural history controls or patients serving as own controls.*

With Negative Recommendations			
ESO/EAN (2021) *European Stroke Organization / European Academy of Neurology*	Post-stroke cognitive impairment	Nootropics *(including cerebrolysin)*	In patients with post-stroke cognitive impairment (PSCI) there is continued uncertainty over the benefits and risks of cerebrolysin. The available evidence suggests that any cognitive benefits of cerebrolysin are likely to be modest and there is risk of serious adverse events with treatment. Considering the balance of risks and harms, we suggest ***against using these agents for PSCI***. ***Quality of evidence:*** *Very low*[+++] ***Strength of recommendation:*** *No recommendation*[+++] [+++]Based on GRADE
AHA (2019) *American Heart Association* *(Derived AHA recommendation from Muresanu, 2022)*	Stroke (*unspecified*)	Neuroprotective Agents (*Not specific to cerebrolysin*)	***The guideline does not recommend*** the administration of any medicative and non-medicative agents with an assumed neuroprotective activity in the acute phase of ischemic stroke. Level of Recommendation: • **III-A** ○ Level of Evidence A: *Data derived from multiple randomized, clinical trials or meta-analyses* ○ Class III: *Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful*
AHA (2019) *American Heart Association*	Acute Ischemic Stroke	Neuroprotective drugs (*Not specific to cerebrolysin*)	At present, pharmacological or nonpharmacological treatments with putative neuroprotective actions ***are not recommended.*** Level of Recommendation: • **III-A** ○ Level of Evidence A: *Data derived from multiple randomized, clinical trials or meta-analyses*

			○ Class III: *Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful*
Discretion of the Attending Physician			
SSP (2014)* ***Stroke Society of the Philippines***	Acute Ischemic Stroke	Neurorestorative & Neuroprotective drugs	The use of drugs with neurorestorative and neuroprotective properties (*i.e.*, ***cerebrolysin***, *citicoline, NeuroAID*) in acute stroke ***remains a matter of preference of the attending physician.*** **No level of evidence/recommendation**
WFNR (2020) ***World Federation for Neurorehabilitation***	Stroke (*unspecified*)	Drugs to enhance recovery (i.e., cerebrolysin)	Individualized treatment decisions (e.g. for l-dopa, fluoxetine, or ***cerebrolysin***) ***are at the discretion of the physician in charge***, mostly as "off-label" treatment. **No level of evidence/recommendation**
****** The only LOCAL CPG***			