

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cerebrolysin

A standardized enzymatic hydrolysate of porcine brain tissue yielding low-molecular-weight neuropeptides and free amino acids that cross the blood-brain barrier and exert neurotrophic, neuroprotective, and neuroplasticity-promoting effects across stroke, traumatic brain injury, and neurodegenerative disease models.

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ABSTRACT

Cerebrolysin is a standardized, injectable preparation of enzymatically derived low-molecular-weight neuropeptides and free amino acids obtained from porcine brain tissue, manufactured by EVER Neuro Pharma (formerly EBEWE Pharma) in Unterach, Austria. The preparation contains peptide fragments exclusively below 10,000 Daltons in molecular weight, including sequences homologous to brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF), together with approximately 15 percent free amino acids by mass. First developed in 1949 by Gerhard Harrer at the University of Graz and subsequently refined through enzymatic hydrolysis standardization at EBEWE Pharma beginning in 1972, the compound has been registered as a pharmaceutical product in over 50 countries (excluding the United States, Canada, the United Kingdom, and most Western European Union member states) for indications including stroke recovery, traumatic brain injury, and dementia syndromes.

The pharmacological profile of Cerebrolysin is characterized by multimodal neurotrophic and neuroprotective activity. The constituent peptides activate tropomyosin receptor kinase (Trk) signaling pathways, particularly TrkA and TrkB, initiating downstream MAPK/ERK and PI3K/Akt cascades that regulate neuronal survival, differentiation, and synaptic plasticity. Additional characterized mechanisms include inhibition of calpain-mediated cytoskeletal degradation, suppression of excitotoxic glutamate signaling, reduction of free radical

formation, attenuation of microglial activation, and promotion of neurogenesis in the subventricular zone and hippocampal dentate gyrus. The low molecular weight of the constituent peptides permits transit across the blood-brain barrier, a property that distinguishes Cerebrolysin from recombinant full-length neurotrophic factors that do not achieve meaningful central nervous system concentrations after peripheral administration.

The clinical evidence base encompasses more than 200 clinical studies involving over 10,000 patients across stroke, traumatic brain injury, Alzheimer's disease, vascular dementia, and pediatric neurodevelopmental indications. The Cerebrolysin and Recovery After Stroke (CARs) randomized, placebo-controlled, double-blind multicenter trial demonstrated large superiority of Cerebrolysin (30 mL per day for 21 days) over placebo on the Action Research Arm Test at day 90 (Mann-Whitney estimator 0.71, 95 percent confidence interval 0.63 to 0.79, P less than 0.0001). The Cerebrolysin Acute Stroke Treatment in Asia (CASTA) trial in 1,070 patients did not demonstrate superiority on the primary endpoint (National Institutes of Health Stroke Scale at day 90), although post hoc analysis in severe stroke (NIHSS greater than 12) showed a trend favoring Cerebrolysin. In Alzheimer's disease, a meta-analysis of randomized controlled trials demonstrated significant improvement in cognitive function (standardized mean difference negative 0.40 on the ADAS-cog at 4 weeks) and global clinical change compared to placebo, with safety comparable to placebo. In traumatic brain injury, 27 clinical studies enrolling 9,752 patients have demonstrated improvements in consciousness level, cognitive performance, and neurological outcomes.

The safety profile across controlled clinical trials is favorable, with adverse event rates comparable to placebo in most analyses. The principal adverse events are vertigo, agitation, feeling hot, headache, and dizziness. Rare anaphylactic reactions have been reported. The compound is contraindicated in epilepsy and severe renal impairment. This monograph reviews the composition, manufacturing, and quality standardization of Cerebrolysin; the multimodal neurotrophic and neuroprotective pharmacology; the pharmacokinetic profile including blood-brain barrier penetration; the clinical evidence base across all studied indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five neurotrophic or neuroprotective alternatives (Cortexin, P21, NSI-189, Actovegin, Semax) against Cerebrolysin on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Product name: Cerebrolysin.

Marketed names: Cerebrolysin (EVER Neuro Pharma; Austria, Russia, China, South Korea, Philippines, Mexico, and approximately 50 additional jurisdictions). The compound is also marketed under the brand name Renacenz in certain Asian markets.

Development code: FPF 1070 (EBEWE Pharma internal designation). The development code appears in the earliest clinical pharmacology literature and in the original Austrian registration dossier.

Chemical Abstracts Service registry number: The compound is a complex biological mixture and does not carry a single CAS registry number. DrugBank identifier DB16599 is the principal database accession.

International Union of Pure and Applied Chemistry name: Not applicable. Cerebrolysin is a defined biological mixture, not a single chemical entity. The pharmacopoeial identity is established by the manufacturing process specification, the molecular weight distribution profile (all components below 10,000 Daltons), the amino acid composition, and the peptide fingerprint by high-performance liquid chromatography.

ATC classification: N06BX (other psychostimulants and nootropics). The Anatomical Therapeutic Chemical code reflects the regulatory positioning of the compound as a neurotrophic agent for cognitive and neurological indications.

1.2 Structural class and chemistry

Cerebrolysin is a biological product, not a single-molecule pharmaceutical. It belongs to the structural class of enzymatic tissue hydrolysates, specifically porcine brain-derived peptide mixtures. The compound is distinguished from other members of this class (Cortexin, Actovegin, Solcoseryl) by its tissue source (whole porcine brain versus cerebral cortex alone or calf blood), its enzymatic hydrolysis protocol, and its peptide molecular weight distribution.

Composition: The preparation contains approximately 85 percent peptides and 15 percent free amino acids by dry weight. The peptide fraction consists of fragments with molecular weights predominantly between 600 and 6,000 Daltons, with an upper limit of 10,000 Daltons enforced by ultrafiltration during manufacturing. Proteomic characterization by nano-liquid chromatography coupled to tandem mass spectrometry has identified peptide fragments homologous to brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), enkephalins, orexin, and galanin [1, 2]. The amino acid composition is dominated by alanine, leucine, lysine, and glutamic acid residues.

Physical properties: Amber to yellow aqueous solution. The commercial preparation is supplied at a concentration of 215.2 mg/mL of Cerebrolysin concentrate in aqueous solution, equivalent to approximately 182.8 mg/mL of peptides and amino acids. The pH of the commercial solution is approximately 7.0 to 7.5. The solution is isotonic and is supplied in glass ampules of 1, 2, 5, 10, 20, and 30 mL volumes. No lyophilized form is commercially available; the preparation is supplied exclusively as a ready-to-use aqueous solution for injection.

Standardization: Batch-to-batch consistency is maintained through the standardized enzymatic hydrolysis protocol, ultrafiltration, and quality control testing that includes amino acid analysis, peptide molecular weight distribution by size-exclusion chromatography, high-performance liquid chromatography fingerprinting, sterility testing, endotoxin testing, and biological activity assays. The EVER Neuro Pharma manufacturing process specification defines the identity and potency of the product [3].

1.3 Manufacturing process

The manufacturing of Cerebrolysin proceeds through four principal stages: tissue preparation, enzymatic hydrolysis, ultrafiltration, and formulation [3, 4].

Tissue preparation: Porcine brain tissue is obtained from veterinary-inspected animals in accordance with European Pharmacopoeia and European Union transmissible spongiform encephalopathy regulatory requirements. The tissue is homogenized in aqueous buffer.

Enzymatic hydrolysis: The homogenate is subjected to controlled proteolytic digestion using defined pancreatic protease preparations. The original acid hydrolysis method (used from 1949 to 1972) was replaced by enzymatic hydrolysis in 1972 to improve batch consistency and to preserve bioactive peptide sequences that acid hydrolysis would destroy. The enzymatic conditions (temperature, pH, enzyme-to-substrate ratio, incubation time) are standardized to produce a reproducible molecular weight distribution.

Ultrafiltration: The hydrolysate is ultrafiltered through membranes with a nominal molecular weight cutoff of 10,000 Daltons to remove residual proteins, large peptide fragments, and cellular debris. The filtrate contains the active peptide fraction and free amino acids.

Formulation: The ultrafiltrate is adjusted to the target concentration (215.2 mg/mL), adjusted to physiological pH, sterile-filtered, and aseptically filled into glass ampules. The final product is terminally sterilized by autoclaving where compatible with product stability, or is manufactured under aseptic conditions with terminal sterility testing.

2. Abstract

Cerebrolysin (FPF 1070) is a standardized preparation of enzymatically derived low-molecular-weight neuropeptides and free amino acids obtained from porcine brain tissue, manufactured by EVER Neuro Pharma in Unterach, Austria, and registered as a pharmaceutical product in over 50 countries for indications that include ischemic stroke recovery, traumatic brain injury, Alzheimer's disease, and vascular dementia [3, 4]. The compound is not approved by the United States Food and Drug Administration, the European Medicines Agency (through centralized procedure), Health Canada, or the United Kingdom Medicines and Healthcare Products Regulatory Agency. It is principally used in Central and Eastern Europe, Russia, China, South Korea, the Philippines, Mexico, and selected Latin American and Middle Eastern jurisdictions.

The pharmacological profile is characterized by multimodal neurotrophic and neuroprotective activity mediated through activation of Trk receptor signaling (particularly TrkA and TrkB), downstream MAPK/ERK and PI3K/Akt pathway engagement, inhibition of calpain-mediated cytoskeletal degradation, suppression of excitotoxic glutamate signaling, attenuation of neuroinflammation through microglial modulation, and promotion of neurogenesis and synaptic plasticity [5, 6, 7]. The low molecular weight of the constituent peptides (below 10,000 Daltons) permits transit across the blood-brain barrier, distinguishing Cerebrolysin from recombinant full-length neurotrophic factors.

The clinical evidence base is extensive in volume but heterogeneous in quality. The CARS trial (Cerebrolysin and Recovery After Stroke) demonstrated large superiority of Cerebrolysin over placebo on motor function recovery after stroke [8]. The CASTA trial (Cerebrolysin Acute Stroke Treatment in Asia) in 1,070 patients did not demonstrate superiority on the primary endpoint [9]. Meta-analyses in Alzheimer's disease demonstrate significant cognitive improvement on the ADAS-cog scale compared to placebo [10, 11]. In traumatic brain injury, pooled evidence from 27 clinical studies supports improvements in consciousness, cognition, and neurological function [12]. The compound is well tolerated, with adverse event rates comparable to placebo in controlled trials; the principal adverse events are vertigo, agitation, headache, and dizziness [13].

The regulatory and scientific positioning of Cerebrolysin is characterized by a tension between the extensive clinical use (over 50 countries, decades of clinical experience) and the absence of approval in the major Western regulatory jurisdictions, which reflects both the regulatory complexity of biological mixture products and the heterogeneity of the clinical trial results. This monograph presents the evidence base as it stands, noting both the positive clinical signals and the methodological limitations.

3. Discovery and Development History

3.1 Origin

Cerebrolysin was first developed in 1949 by Gerhard Harrer at the University of Graz, Austria, as a porcine brain-derived extract for the treatment of traumatic brain injury and metabolic brain failure in post-war Austrian hospitals [4, 14]. The original formulation was produced by acid hydrolysis of porcine brain tissue followed by filtration to isolate low-molecular-weight fractions. The rationale was that brain tissue contained endogenous neurotrophic and neuroprotective factors that, if administered parenterally in a form capable of crossing the blood-brain barrier, could support neuronal survival and functional recovery after brain injury.

3.2 Early clinical use and EBEWE Pharma

By 1954, EBEWE Pharma (Unterach, Austria) began commercial production of Cerebrolysin, making it available across Central European hospitals [4]. The early formulation was crude by modern standards; batch consistency was poor, and the peptide composition varied depending on enzymatic activity during tissue processing. Clinical use in this period was based on observational evidence and uncontrolled case series rather than randomized clinical trials.

3.3 Standardization through enzymatic hydrolysis (1972)

A transformative advance occurred in 1972 when EBEWE Pharma implemented enzymatic hydrolysis protocols that replaced the original acid-based extraction method [3, 4]. Enzymatic hydrolysis using pancreatic proteases produced peptide fragments with reproducible molecular weight distributions and amino acid sequences, eliminating the batch-to-batch variability that characterized earlier formulations. The standardized product contained a defined mixture of neuropeptides and free amino acids with molecular weights predominantly between 600 and 6,000 Daltons, including fragments homologous to BDNF, NGF, and CNTF. This standardization was the technical foundation for the subsequent clinical trial program.

3.4 Clinical development and regulatory expansion

Beginning in the 1980s and accelerating through the 1990s and 2000s, Cerebrolysin was evaluated in a series of randomized, placebo-controlled clinical trials across stroke, traumatic brain injury, Alzheimer's disease, and vascular dementia [8, 9, 10, 11, 12]. The compound received marketing authorization in Austria, Russia, China, South Korea, the Philippines, Mexico, and numerous additional jurisdictions. The manufacturer, EBEWE Pharma, was acquired by the Lannacher Heilmittel group and subsequently became part of the EVER Pharma group (now EVER Neuro Pharma), which continues to manufacture and market the product.

3.5 Proteomic characterization

The proteomic composition of Cerebrolysin was substantially characterized through advances in mass spectrometry and liquid chromatography beginning in the early 2000s. Nano-liquid chromatography coupled to tandem mass spectrometry identified specific peptide fragments including sequences homologous to BDNF, NGF, GDNF, CNTF, enkephalins, orexin, and galanin [1, 2]. This molecular characterization provided a mechanistic basis for the observed neurotrophic and neuroprotective activities and supported the development of quality control methods based on peptide fingerprinting.

3.6 Current regulatory and scientific status

Cerebrolysin is registered as a pharmaceutical product in over 50 countries but is not approved by the FDA, EMA (centralized procedure), Health Canada, or UK MHRA. The compound has been the subject of controversy regarding both the quality of some clinical trials and the relationship between the manufacturer and certain clinical investigators [15]. The Cochrane Collaboration has published systematic reviews of Cerebrolysin in vascular dementia (Chen et al., 2013) and in acute ischemic stroke, concluding that the evidence is insufficient to recommend routine use but that the safety profile is acceptable [16]. The compound remains in active clinical use in registered jurisdictions and is the subject of ongoing clinical investigation.

4. Mechanism of Action

Cerebrolysin is a multi-component biological product whose pharmacological activity reflects the combined effects of multiple peptide fragments acting on multiple molecular targets. The characterized mechanisms of action include neurotrophic factor receptor activation, neuroprotective signaling, anti-excitotoxic activity, anti-inflammatory effects, and neurogenesis promotion [5, 6, 7].

4.1 Neurotrophic factor receptor activation

The peptide fragments in Cerebrolysin that are homologous to BDNF and NGF activate the tropomyosin receptor kinase (Trk) family, particularly TrkA (the high-affinity NGF receptor) and TrkB (the high-affinity BDNF receptor) [5, 6]. Activation of these receptor tyrosine kinases initiates autophosphorylation and recruitment of adaptor proteins (Shc, FRS2, PLCgamma1) that activate three principal downstream signaling cascades:

The MAPK/ERK pathway (Ras-Raf-MEK-ERK): promotes neuronal differentiation, neurite outgrowth, and synaptic plasticity through transcriptional regulation of immediate early genes and cytoskeletal remodeling proteins.

The PI3K/Akt pathway: promotes neuronal survival through phosphorylation and inactivation of pro-apoptotic proteins (Bad, Bax, caspase-9) and through activation of the mTOR pathway supporting protein synthesis and cellular growth.

The PLCgamma/PKC pathway: modulates intracellular calcium signaling and synaptic transmission.

In vitro studies in primary cortical and hippocampal neuronal cultures have demonstrated that Cerebrolysin produces concentration-dependent activation of ERK1/2 phosphorylation, Akt phosphorylation, and CREB (cAMP response element-binding protein) phosphorylation [5]. These effects are partially blocked by Trk receptor inhibitors (K252a), confirming the involvement of Trk-mediated signaling.

4.2 Neuroprotective mechanisms

Cerebrolysin exerts neuroprotective effects through multiple mechanisms that converge on the prevention of neuronal death in the context of ischemia, excitotoxicity, and oxidative stress [6, 7]:

Anti-excitotoxic activity: Cerebrolysin reduces glutamate-induced excitotoxicity in neuronal cultures by modulating NMDA receptor signaling and by reducing intracellular calcium overload. The mechanism involves both direct effects on glutamate receptor function and indirect effects through stabilization of intracellular calcium buffering systems.

Anti-apoptotic activity: Through PI3K/Akt pathway activation, Cerebrolysin inhibits the mitochondrial apoptotic pathway by phosphorylating and inactivating Bad and by maintaining mitochondrial membrane potential. Caspase-3 activation is reduced in Cerebrolysin-treated neuronal cultures exposed to oxygen-glucose deprivation [7].

Calpain inhibition: Cerebrolysin inhibits calpain-mediated degradation of the cytoskeletal protein MAP2 (microtubule-associated protein 2) in neuronal cultures subjected to calcium overload [17]. This mechanism preserves dendritic architecture and synaptic connectivity during ischemic and excitotoxic insults.

Antioxidant effects: Cerebrolysin reduces free radical formation and lipid peroxidation in models of cerebral ischemia, although the compound does not function as a direct radical scavenger. The antioxidant effect is primarily indirect, through stabilization of mitochondrial function and through upregulation of endogenous antioxidant enzyme systems (superoxide dismutase, catalase, glutathione peroxidase).

4.3 Anti-inflammatory effects

Cerebrolysin attenuates neuroinflammation through modulation of microglial activation [6]. In models of cerebral ischemia and traumatic brain injury, Cerebrolysin reduces the activation of microglia from the resting (ramified) state to the activated (amoeboid) state and shifts the microglial phenotype from the pro-inflammatory M1 polarization toward the neuroprotective M2 polarization. Downstream consequences include reduced production of pro-inflammatory cytokines (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6) and reduced expression of in-

ducible nitric oxide synthase. The molecular basis for the microglial modulation is not fully characterized but plausibly involves the neurotrophic factor receptor signaling pathways described in section 4.1.

4.4 Neurogenesis and neuroplasticity

Cerebrolysin promotes neurogenesis in the subventricular zone and hippocampal dentate gyrus in rodent models of cerebral ischemia and in aged animals [18, 19]. The neurogenic effect is associated with increased expression of doublecortin (a marker of immature migrating neurons) and increased BrdU incorporation (a marker of cell proliferation) in the neurogenic niches. The newly generated neurons show evidence of functional integration, including dendritic arborization and synapse formation with existing cortical circuits.

In addition to de novo neurogenesis, Cerebrolysin promotes synaptic plasticity through increased expression of synaptophysin and postsynaptic density protein 95 (PSD-95), markers of presynaptic and postsynaptic specialization respectively [19]. Long-term potentiation, the electrophysiological correlate of learning and memory, is enhanced by Cerebrolysin treatment in hippocampal slice preparations.

4.5 Composite pharmacology

The composite pharmacological profile of Cerebrolysin reflects the simultaneous activity of multiple peptide fragments on multiple molecular targets. This multi-target profile is both the principal scientific strength and the principal regulatory weakness of the compound. The strength is that the multi-target activity produces synergistic neuroprotective and neurorestorative effects that exceed what any single neurotrophic factor can achieve. The weakness is that the complexity of the mixture makes it difficult to assign specific effects to specific molecular entities, complicating the regulatory pathway for approval in jurisdictions that require single-entity mechanism-of-action characterization.

5. Pharmacokinetics and Routes of Administration

5.1 General pharmacokinetic considerations

The pharmacokinetics of Cerebrolysin present unique challenges because the compound is a complex mixture of peptides and amino acids rather than a single molecular entity [20]. It has not been possible to measure classical single-compound pharmacokinetic parameters (C_{max}, AUC, clearance, volume of distribution) for the mixture as a whole. Pharmacokinetic characterization has therefore relied on indirect pharmacodynamic measurements, on tracking of specific peptide components, and on measurement of the downstream biological effects as surrogate markers of active compound exposure.

5.2 Absorption and blood-brain barrier penetration

The low molecular weight of the Cerebrolysin peptide components (below 10,000 Daltons, predominantly 600 to 6,000 Daltons) is the critical property enabling blood-brain barrier penetration [3, 5]. Full-length neurotrophic factors (BDNF molecular weight approximately 27,000 Daltons; NGF molecular weight approximately 26,500 Daltons as the homodimer) do not cross the blood-brain barrier in therapeutically relevant quantities after peripheral administration, which has been a principal obstacle to the clinical development of recombinant neurotrophic factors. The Cerebrolysin peptide fragments, being substantially smaller, cross the blood-brain barrier through a combination of paracellular diffusion and receptor-mediated transcytosis.

Cerebrospinal fluid studies in preclinical models have demonstrated the presence of Cerebrolysin peptide components in the cerebrospinal fluid following intravenous administration, with CSF concentrations peaking approximately 1 to 2 hours after injection and persisting for 12 to 18 hours, substantially longer than the plasma residence time [20].

5.3 Distribution

Volume of distribution has not been formally characterized for the mixture. The constituent peptides distribute to brain tissue as demonstrated by CSF measurements and by the central nervous system pharmacodynamic effects observed in clinical and preclinical studies. Plasma protein binding of the individual peptide components has not been systematically characterized.

5.4 Metabolism and elimination

The constituent peptides undergo proteolytic degradation by tissue and plasma peptidases, which is the principal elimination mechanism. Some peptide components (particularly those homologous to BDNF) have very short plasma half-lives (on the order of minutes) due to rapid proteolytic clearance [20]. The free amino acid fraction is metabolized through standard amino acid metabolic pathways.

Renal filtration contributes to elimination of the low-molecular-weight peptide fraction, with approximately 60 percent of administered material cleared through glomerular filtration within 6 hours [20]. The overall plasma half-life of the mixture, estimated from pharmacodynamic surrogate measurements, is approximately 2.5 to 6 hours. However, the therapeutic neuroprotective effects persist for 48 to 96 hours after a single dose, reflecting sustained cerebrospinal fluid concentrations and the persistence of downstream signaling cascade activation beyond the period of direct receptor engagement.

5.5 Routes of administration

Cerebrolysin is administered exclusively by parenteral injection. Three routes are used clinically:

Intramuscular injection: Volumes up to 5 mL may be injected undiluted into a large muscle mass (gluteus maximus, deltoid, or vastus lateralis). Injection should be administered slowly over approximately 3 minutes. Intramuscular administration produces a depot effect at the injection site, with sustained release over 2 to 4 hours that effectively extends the elimination half-life compared to intravenous bolus.

Intravenous injection: Volumes up to 10 mL may be administered by slow direct intravenous injection over 3 minutes.

Intravenous infusion: Volumes of 10 to 50 mL are administered by slow intravenous infusion, diluted in 100 mL of compatible infusion solution (0.9 percent sodium chloride, Ringer's solution, or 5 percent glucose solution) and infused over 15 to 60 minutes. This is the preferred route for higher-dose clinical protocols (30 to 50 mL daily) used in stroke and traumatic brain injury indications.

Oral administration is not feasible owing to the peptide nature of the active constituents, which would be degraded by gastrointestinal proteases before absorption. Subcutaneous administration has been used in some research contexts but is not a registered route.

5.6 Special populations

Renal impairment: The compound is contraindicated in severe renal impairment owing to the renal contribution to peptide clearance and the risk of accumulation. Dose adjustment is recommended in moderate renal impairment.

Hepatic impairment: The peptide nature of the compound means that hepatic cytochrome P450 metabolism does not contribute substantially to clearance. Hepatic impairment is not expected to materially alter the pharmacokinetics.

Pediatric populations: Cerebrolysin has been studied in pediatric populations for neurodevelopmental indications with dose adjustment based on body weight. Safety data in pediatric populations are limited but have not identified pediatric-specific safety concerns beyond those observed in adults.

Geriatric populations: No specific dose adjustment is recommended for geriatric populations in the absence of renal impairment.

6. Preclinical Pharmacology

6.1 In vitro neuroprotection

Cerebrolysin has been extensively studied in primary neuronal cultures and in neuronal cell lines subjected to various forms of injury. In primary rat cortical neurons exposed to oxygen-glucose deprivation (an in vitro model of ischemic stroke), Cerebrolysin at concentrations equivalent to clinically achieved CSF levels (10 to 100 micrograms per milliliter) reduced neuronal death by 40 to 60 percent compared to untreated controls [7]. The protective effect was associated with preservation of mitochondrial membrane potential, reduction of caspase-3 activation, and maintenance of MAP2-positive dendritic architecture.

In glutamate excitotoxicity models, Cerebrolysin reduced calcium influx through NMDA receptor channels and prevented the downstream activation of calpain and caspase cascades [6, 17]. The anti-excitotoxic activity was concentration-dependent and was partially attenuated by the Trk receptor inhibitor K252a, indicating that both Trk-dependent and Trk-independent mechanisms contribute.

6.2 In vivo stroke models

In the middle cerebral artery occlusion (MCAO) model of focal cerebral ischemia in rats, Cerebrolysin administered intravenously at 2.5 to 7.5 mL/kg within 4 hours of occlusion produced significant reductions in infarct volume (30 to 50 percent reduction versus vehicle) and significant improvement in neurological deficit scores [18, 19]. The neuroprotective effect was accompanied by increased expression of BDNF and NGF in the peri-infarct cortex, increased neurogenesis in the subventricular zone, and increased synaptogenesis as measured by synaptophysin immunoreactivity.

The therapeutic time window for neuroprotective efficacy in the MCAO model extends to approximately 4 to 6 hours after occlusion onset, beyond which the neuroprotective effect diminishes. This preclinical finding informed the clinical trial design, in which Cerebrolysin treatment was typically initiated within 12 to 72 hours of stroke onset.

6.3 Traumatic brain injury models

In controlled cortical impact and weight-drop models of traumatic brain injury in rats and mice, Cerebrolysin reduced lesion volume, attenuated cerebral edema, improved neurological function scores, and reduced blood-brain barrier disruption [12]. The effects were associated with reduced microglial activation (decreased Iba-1 immunoreactivity) and reduced expression of pro-inflammatory cytokines in the perilesional cortex.

6.4 Alzheimer's disease models

In transgenic mouse models of Alzheimer's disease (APP/PS1 double transgenic mice, Tg2576 mice), chronic Cerebrolysin administration reduced amyloid plaque burden, decreased soluble amyloid-beta 42 levels, and improved performance on the Morris water maze and novel object recognition tests [21]. The anti-amyloid effect was associated with increased alpha-secretase activity (promoting the non-amyloidogenic processing pathway) and with reduced beta-secretase (BACE1) expression. Whether these preclinical anti-amyloid effects translate to clinically meaningful disease modification in human Alzheimer's disease remains an open question; the clinical trial evidence to date demonstrates symptomatic cognitive improvement but has not demonstrated amyloid biomarker modification.

6.5 Neurogenesis studies

The Zhang et al. (2010) and Rockenstein et al. (2007) studies demonstrated that Cerebrolysin promotes neurogenesis in the adult rodent brain, both under physiological conditions and after ischemic or traumatic injury [18, 19]. Newly generated neurons in the subventricular zone migrated to the peri-infarct cortex and showed evidence of functional integration, including expression of mature neuronal markers (NeuN), dendritic arborization, and synapse formation with existing cortical circuits. The neurogenic effect was dependent on BDNF-TrkB signaling, as it was attenuated by TrkB receptor blockade.

7. Clinical Evidence Base

7.1 Ischemic stroke

The clinical evidence for Cerebrolysin in ischemic stroke is extensive but heterogeneous. The two landmark trials are CASTA and CARS.

CASTA trial (Cerebrolysin Acute Stroke Treatment in Asia): This randomized, double-blind, placebo-controlled trial enrolled 1,070 patients with acute ischemic stroke at 52 centers across Asia [9]. Patients received Cerebrolysin 30 mL/day or placebo (saline) intravenously for 10 days, beginning within 12 hours of stroke onset. The primary endpoint was the National Institutes of Health Stroke Scale (NIHSS) score at day 90. The trial did not demonstrate a statistically significant difference between Cerebrolysin and placebo on the primary endpoint (NIHSS improvement 6.0 versus 5.7 points, $P = 0.34$). Post hoc analysis stratified by baseline severity showed a trend favoring Cerebrolysin in patients with severe stroke (NIHSS greater than 12 at baseline), but this subgroup analysis did not reach statistical significance after correction for multiple comparisons.

CARS trial (Cerebrolysin and Recovery After Stroke): This randomized, placebo-controlled, double-blind, multicenter trial enrolled patients with acute ischemic stroke and upper-limb motor deficit during early rehabilitation [8]. Patients received Cerebrolysin 30 mL/day or placebo (saline) intravenously for 21 days, beginning 24 to 72 hours after stroke onset, combined with a standardized 21-day rehabilitation program. The primary endpoint was the Action Research Arm Test (ARAT) score at day 90. The trial demonstrated large superiority of Cerebrolysin over placebo (Mann-Whitney estimator 0.71, 95 percent confidence interval 0.63 to 0.79, P less than 0.0001). The multivariate effect size on global status, assessed using 12 different outcome scales, indicated small-to-medium superiority of Cerebrolysin (Mann-Whitney estimator 0.62, 95 percent confidence interval 0.58 to 0.65, P less than 0.0001).

Meta-analysis evidence: A meta-analysis of nine randomized clinical trials of Cerebrolysin in early post-stroke recovery (Bornstein et al., 2018) concluded that Cerebrolysin was safe and showed benefit on motor function endpoints, particu-

larly when combined with standardized rehabilitation [22]. A separate meta-analysis of the CARS trials (Muresanu et al., 2017) confirmed the benefit on motor function recovery [23].

Interpretation: The discrepancy between the negative CASTA result and the positive CARS result has been attributed to several methodological differences: CASTA treated for 10 days versus 21 days in CARS; CASTA initiated treatment within 12 hours versus 24 to 72 hours in CARS; and CARS mandated a standardized rehabilitation program whereas CASTA did not [24]. The emerging interpretation is that Cerebrolysin may be most effective as an adjunct to structured rehabilitation rather than as a standalone acute neuroprotective agent.

7.2 Traumatic brain injury

The clinical efficacy of Cerebrolysin in traumatic brain injury has been assessed in 27 clinical studies with durations of up to 6 months, enrolling a total of 9,752 patients [12]. The evidence encompasses mild, moderate, and severe TBI.

Mild TBI: Chen et al. (2013) reported a double-blind, placebo-controlled, randomized study demonstrating that Cerebrolysin improved cognitive function in mild TBI patients at 3 months after injury, with particular improvement in long-term memory and drawing function [25].

Moderate-to-severe TBI: Wong et al. (2017) reported a multicenter trial in which Cerebrolysin 30 mL/day for 10 days, initiated within 24 hours of injury, improved Glasgow Outcome Scale Extended scores at 6 months compared to placebo, with the greatest benefit observed in patients with moderate TBI (GCS 9 to 12) [12].

7.3 Alzheimer's disease

Individual trials: Ruether et al. (2001) reported a multicenter, randomized, double-blind, placebo-controlled trial in which patients with mild-to-moderate Alzheimer's disease received Cerebrolysin 30 mL intravenously five days per week for four weeks or placebo [26]. At week 4, the Cerebrolysin group showed significant improvement on the ADAS-cog (the principal cognitive outcome measure in Alzheimer's disease trials) compared to placebo. At week 12, the between-group difference on the Clinician's Interview-Based Impression of Change (CIBIC+) reached statistical significance in favor of Cerebrolysin.

Combination therapy: Alvarez et al. (2011) studied the combination of Cerebrolysin with donepezil in a randomized, controlled trial and reported that the combination produced greater cognitive improvement on the ADAS-cog than donepezil alone, suggesting additive or synergistic effects through complementary mechanisms (neurotrophic support plus cholinesterase inhibition) [27].

Meta-analysis: Gauthier et al. (2015) published a meta-analysis of randomized controlled clinical trials of Cerebrolysin in mild-to-moderate Alzheimer's disease [10]. The analysis demonstrated that Cerebrolysin was significantly more effective than placebo at 4 weeks regarding cognitive function (standardized mean difference negative 0.40 points, 95 percent confidence interval negative 0.66 to negative 0.13, $P = 0.0031$) and at 4 weeks and 6 months regarding global clinical change. The safety profile was comparable to placebo.

7.4 Vascular dementia

Guekht et al. (2011) reported a large multicenter, double-blind, placebo-controlled study involving 242 patients with vascular dementia [28]. Patients received Cerebrolysin 20 mL intravenously five days per week for four weeks (two treatment courses separated by eight weeks). The primary endpoint was the combined outcome of cognition (ADAS-cog+ score) and global clinical function (CIBIC+ score) at week 24. The ADAS-cog+ score improved by 10.6 points in the Cerebrolysin group compared to 4.4 points in the placebo group, a clinically and statistically significant difference. The Cochrane systematic review of Cerebrolysin for vascular dementia (Chen et al., 2013) concluded that there was some evidence of benefit on cognitive function but that the quality of the evidence was insufficient to make definitive recommendations [16].

7.5 Pediatric neurodevelopmental indications

Cerebrolysin has been studied in pediatric populations for autism spectrum disorder, cerebral palsy, and perinatal brain injury in several jurisdictions, principally in Russia and in Eastern European and Asian countries [29]. The evidence base for these applications is limited in volume and quality by Western regulatory standards, consisting principally of open-label studies and small randomized trials. The safety data in pediatric populations have not identified pediatric-specific safety concerns beyond those observed in adults.

8. Sourcing and Quality Verification

Pharmaceutical-grade Cerebrolysin is manufactured exclusively by EVER Neuro Pharma (Unterach, Austria) and is distributed through authorized pharmaceutical distributors in registered jurisdictions. The compound is supplied as a ready-to-use injectable solution in glass ampules (1, 2, 5, 10, 20, and 30 mL volumes) at a concentration of 215.2 mg/mL.

Authenticity verification: Because Cerebrolysin is a complex biological mixture rather than a single chemical entity, authenticity verification differs from that of small-molecule pharmaceuticals. The principal methods are:

- Verification of packaging, labeling, and batch number against manufacturer records
- Amino acid composition analysis by high-performance liquid chromatography or ion-exchange chromatography, compared to the reference profile established by the manufacturer
- Peptide fingerprinting by reversed-phase high-performance liquid chromatography, compared to the reference chromatographic profile
- Size-exclusion chromatography confirmation that all peptide components are below 10,000 Daltons
- Sterility and endotoxin testing for parenteral preparations

Counterfeit risk: The compound is subject to counterfeiting in markets with weak pharmaceutical regulatory enforcement. Investigators and clinicians should obtain Cerebrolysin only through authorized pharmaceutical distribution channels and should verify batch authenticity through the manufacturer's verification system where available.

Research-grade alternatives: No validated research-grade Cerebrolysin is available from independent chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical). The pharmaceutical product is the sole validated source. Investigators requiring the compound for research applications should obtain it through authorized pharmaceutical channels or through direct arrangement with the manufacturer.

Quality considerations: Batch-to-batch consistency is maintained through the standardized manufacturing process, but investigators should be aware that the inherent complexity of a biological mixture product means that minor variations in peptide composition may occur between batches, even within specification. For research applications where precise dose-response characterization is critical, investigators should use material from a single batch throughout a study and should archive aliquots for retrospective quality verification.

9. Reconstitution and Handling

Cerebrolysin is supplied as a ready-to-use aqueous solution and does not require reconstitution. The commercial preparation at 215.2 mg/mL is isotonic and can be administered directly by intramuscular injection (up to 5 mL) or by slow intravenous injection (up to 10 mL).

Dilution for intravenous infusion: For doses of 10 to 50 mL, the preparation must be diluted in 100 mL of a compatible infusion solution prior to intravenous infusion. Compatible solutions include 0.9 percent sodium chloride (normal saline), Ringer's solution, and 5 percent glucose solution. The diluted preparation should be infused within 15 to 60 minutes of preparation.

Incompatibilities: Cerebrolysin should not be mixed with other drugs in the same infusion container. Specifically, the manufacturer advises against mixing with vitamins, cardiovascular drugs, or other peptide preparations. Solutions containing high concentrations of lipids or amino acids (such as parenteral nutrition solutions) should not be used as diluents.

Storage: Unopened ampules should be stored at controlled room temperature (15 to 25 degrees Celsius) protected from light. The amber solution is light-sensitive; prolonged exposure to direct light may degrade the peptide components. Refrigerated storage (2 to 8 degrees Celsius) is acceptable but not required for the unopened product.

Stability after opening: The preparation is for single use only. Any unused portion remaining in the ampule after a single administration should be discarded. The product does not contain preservatives, and microbial contamination of the opened ampule represents a risk for multi-dose use.

Stability of diluted preparation: The diluted infusion solution should be used immediately after preparation or within 4 hours if stored at controlled room temperature. The diluted preparation should not be refrigerated or frozen.

Visual inspection: Prior to administration, the solution should be inspected visually for particulate matter and discoloration. The normal appearance is a clear to slightly opalescent amber to yellow solution. Solutions that appear turbid, contain

visible particulates, or show color change from the expected amber-yellow should not be administered.

10. Stack Interactions and Combinations

Cerebrolysin interacts with several drug classes through its neurotrophic and neuroprotective pharmacology. Because the compound is a peptide mixture that is not metabolized by cytochrome P450 enzymes, classical pharmacokinetic drug-drug interactions mediated by CYP inhibition or induction are not expected. Interactions are therefore predominantly pharmacodynamic.

Cholinesterase inhibitors (donepezil, rivastigmine, galantamine): The combination of Cerebrolysin with cholinesterase inhibitors has been studied in Alzheimer's disease clinical trials and has demonstrated additive or synergistic cognitive improvement [27]. The mechanistic rationale is that Cerebrolysin provides neurotrophic support for cholinergic neurons while cholinesterase inhibitors increase synaptic acetylcholine availability. The combination is well tolerated and is used in clinical practice in registered jurisdictions.

Memantine: The combination of Cerebrolysin with the NMDA receptor antagonist memantine has not been extensively studied in clinical trials but has preclinical support. The mechanisms are complementary: Cerebrolysin provides neurotrophic support while memantine reduces excitotoxic glutamate signaling. No pharmacokinetic interaction is expected.

Antidepressants: Cerebrolysin has been studied in combination with selective serotonin reuptake inhibitors (SSRIs) for post-stroke depression, with some evidence of additive benefit [30]. No pharmacokinetic interaction mediated by CYP enzymes is expected because the peptide components of Cerebrolysin are not CYP substrates or inhibitors.

Anticoagulants and antiplatelet agents: No interaction between Cerebrolysin and anticoagulant or antiplatelet therapy has been reported. The compound does not affect coagulation parameters. Concurrent use with standard post-stroke antithrombotic therapy (aspirin, clopidogrel, warfarin, direct oral anticoagulants) is routine in registered jurisdictions.

Antiepileptic drugs: Cerebrolysin is contraindicated in patients with epilepsy owing to a theoretical risk of lowering the seizure threshold through neurotrophic and neurogenesis-promoting mechanisms. Concurrent use with antiepileptic drugs (valproate, carbamazepine, levetiracetam) should be approached with caution.

Other neurotrophic agents: Concurrent use with other neurotrophic peptide preparations (Cortexin, Semax, Actovegin) is pharmacologically redundant in some aspects and has not been studied in controlled trials. The combination is not recommended owing to the absence of safety and efficacy data for multi-neurotrophic-agent regimens.

Physical incompatibilities: As noted in section 9, Cerebrolysin should not be mixed with other drugs in the same infusion container.

11. Adverse Events and Safety

11.1 Overall safety profile

The safety profile of Cerebrolysin across controlled clinical trials is favorable, with adverse event rates generally comparable to placebo [13]. A pooled safety analysis of clinical trials in dementia and stroke (Alvarez et al., 2011) found no statistically significant difference in the incidence of adverse events between Cerebrolysin-treated and placebo-treated groups [13].

11.2 Common adverse events

The most commonly reported adverse events in controlled clinical trials include:

- Vertigo (2 to 5 percent, versus 1 to 3 percent on placebo)
- Agitation (1 to 4 percent)
- Feeling hot or flushing (1 to 3 percent)
- Headache (2 to 5 percent, versus 2 to 4 percent on placebo)
- Dizziness (1 to 3 percent)
- Nausea (1 to 2 percent)
- Insomnia (1 to 2 percent)
- Injection-site reactions (pain, erythema, induration at the injection site; 1 to 3 percent with intramuscular administration)

These adverse events are generally mild, self-limiting, and do not require treatment discontinuation.

11.3 Serious adverse events

In the CASTA trial, serious adverse events occurred at similar rates in the Cerebrolysin (9.6 percent) and placebo (8.7 percent) groups, with no individual serious adverse event type occurring significantly more frequently in the Cerebrolysin group [9]. In the CARS trial, no treatment-related serious adverse events were reported [8].

An increased rate of spontaneous adverse effects requiring hospitalization has been reported in some stroke trials, although the association with Cerebrolysin has not been established as causal and may reflect the underlying disease severity in the treated population [15].

11.4 Anaphylaxis and hypersensitivity

Anaphylactic reactions to Cerebrolysin are rare but documented. A literature review from China identified 35 cases of anaphylactic reactions from 1994 to 2009, with reactions occurring within minutes to hours after administration [31]. A 2024 case report described a life-threatening anaphylactic reaction to Cerebrolysin in a European patient [32]. The porcine biological origin of the compound means that individuals with pork allergy or sensitivity to porcine-derived products are at heightened risk and should not receive the compound.

11.5 Contraindications

Cerebrolysin is contraindicated in:

- Known hypersensitivity to the compound or to porcine-derived biological products
- Epilepsy (owing to theoretical risk of seizure threshold reduction)
- Severe renal impairment (owing to impaired peptide clearance)
- Status epilepticus

11.6 Long-term safety

Cerebrolysin has been studied for durations of up to three years in dementia indications, with no evidence of cumulative toxicity or late-onset adverse events [10, 13]. The long-term safety profile is consistent with the short-term profile. Weight loss has been reported as an uncommon finding in long-term treatment.

11.7 Pregnancy and lactation

Animal reproductive toxicity studies have not demonstrated teratogenic effects at multiples of the human dose. Human pregnancy data are limited. Use in pregnancy is generally discouraged unless clearly indicated. Lactation data are insufficient to

characterize excretion in human milk.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five neurotrophic or neuroprotective alternatives against Cerebrolysin, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as agents with substantive clinical or preclinical evidence in neurotrophic, neuroprotective, or neurorestorative applications that overlap with the Cerebrolysin indication space.

12.1 Cortexin

Composition and mechanism: Cortexin is a peptide preparation derived from the cerebral cortex of young cattle and pigs, containing low-molecular-weight neuropeptides, amino acids, vitamins, and trace minerals [33]. Like Cerebrolysin, it is a biological mixture rather than a single molecular entity. The peptide fraction includes sequences homologous to BDNF and NGF. The mechanism of action includes neurotrophic factor pathway activation, antioxidant effects, and GABA-ergic modulation.

Novelty: Low. The compound is mechanistically similar to Cerebrolysin and represents the same structural class (tissue-derived peptide hydrolysate). The tissue source (cerebral cortex versus whole brain) and the inclusion of vitamins and trace minerals distinguish the composition but do not represent a fundamentally novel mechanism.

Effect size: Modest. Clinical studies, principally conducted in Russia and Eastern European jurisdictions, have demonstrated cognitive improvement in stroke, TBI, and neurodevelopmental indications, but effect sizes are generally smaller than those reported for Cerebrolysin in comparable indications. Head-to-head comparative data are limited.

Promising potential: Low to moderate. The compound is registered in Russia and several CIS countries but has not been submitted for approval in Western regulatory jurisdictions. The clinical trial quality is heterogeneous, and the regulatory

trajectory is limited to existing markets.

Side-effect profile: Favorable. Adverse events are similar in type and frequency to those observed with Cerebrolysin (headache, dizziness, injection-site reactions). The compound is generally well tolerated.

Overall validation: Low to moderate. The evidence base is smaller and of lower methodological quality than the Cerebrolysin evidence base. The compound serves a similar clinical role in the jurisdictions where it is registered but does not have the international clinical trial infrastructure that supports Cerebrolysin.

Comparison to Cerebrolysin: Cortexin is a less extensively studied compound with a similar mechanism and a smaller evidence base. Cerebrolysin has the advantages of larger clinical trials (CASTA, CARS), meta-analytic evidence, and broader international registration. Cortexin has the practical advantage of lower cost in markets where both are available.

12.2 P21 (CNTF-derived peptide)

Composition and mechanism: P21 is a synthetic 11-amino-acid peptide derived from the active region of ciliary neurotrophic factor (CNTF) [34]. It was designed to mimic the neurotrophic effects of CNTF while avoiding the receptor-binding domain that produces the peripheral side effects (cachexia, anorexia) observed with full-length CNTF. P21 acts through the gp130 receptor to activate the JAK/STAT signaling pathway, promoting neurogenesis and synaptic plasticity, particularly in the hippocampal dentate gyrus.

Novelty: Moderate to high. The single-peptide, rationally designed approach is mechanistically cleaner than the biological mixture approach of Cerebrolysin. The selective targeting of CNTF-like signaling through a truncated peptide is a novel pharmacological strategy.

Effect size: Preclinical only. P21 has demonstrated significant neurogenesis and cognitive improvement in rodent models (Morris water maze, novel object recognition), with effect sizes comparable to or exceeding Cerebrolysin in head-to-head preclinical comparisons [34]. No human clinical data exist.

Promising potential: Moderate. The rationally designed approach and the strong preclinical data support continued investigation. The absence of human clinical data is the principal limitation. The compound is available from research peptide

suppliers but is not registered as a pharmaceutical product in any jurisdiction.

Side-effect profile: Unknown in humans. Preclinical safety data are limited. The designed avoidance of the CNTF receptor-binding domain associated with cachexia is a theoretical safety advantage.

Overall validation: Low. The evidence base is entirely preclinical and originates from a limited number of research groups. No human pharmacokinetic, safety, or efficacy data exist.

Comparison to Cerebrolysin: P21 represents a newer, more targeted approach to neurotrophic peptide pharmacology, but has no clinical validation. Cerebrolysin has the advantages of decades of clinical use, large randomized trials, and regulatory registration. P21 has the theoretical advantage of mechanistic specificity and rational design. The two agents may be complementary in research contexts; Cerebrolysin provides broad neurotrophic support while P21 provides targeted CNTF-pathway activation.

12.3 NSI-189

Composition and mechanism: NSI-189 is a small-molecule (non-peptide) benzylpiperazine-aminopyridine compound developed by Neuralstem for the treatment of major depressive disorder and cognitive impairment [35]. The mechanism of action involves stimulation of hippocampal neurogenesis through a target that is not fully characterized but is distinct from monoamine neurotransmitter pathways. The compound also increases hippocampal volume as measured by magnetic resonance imaging in clinical studies.

Novelty: High. NSI-189 is a small-molecule neurogenesis stimulator with a mechanism distinct from neurotrophic factor signaling. The oral bioavailability and the demonstrated hippocampal volumetric effect in humans distinguish it from peptide-based approaches.

Effect size: Mixed. A Phase 2 randomized, double-blind, placebo-controlled trial in major depressive disorder demonstrated significant improvement on the Symptoms of Depression Questionnaire (SDQ-2) at 40 mg daily but did not demonstrate significance on the primary endpoint (Montgomery-Asberg Depression Rating Scale) at any dose [35]. Cognitive improvement has been reported in exploratory analyses.

Promising potential: Moderate. The compound completed Phase 2 for major depressive disorder with mixed results. The hippocampal volumetric effect is a unique biomarker signal. The compound is not in active clinical development for neurodegenerative indications as of the most recent literature review.

Side-effect profile: Generally well tolerated in Phase 1 and Phase 2 studies. Adverse events included headache, dizziness, and gastrointestinal symptoms at higher doses. No serious safety signals have been identified.

Overall validation: Moderate. Phase 2 clinical data exist but the primary endpoint was not met. The hippocampal neurogenesis mechanism is supported by pre-clinical and clinical biomarker evidence but has not produced a registration-quality clinical outcome.

Comparison to Cerebrolysin: NSI-189 and Cerebrolysin act through fundamentally different mechanisms (small-molecule neurogenesis stimulation versus peptide-mixture neurotrophic support). NSI-189 has the advantage of oral bioavailability. Cerebrolysin has the advantage of broader clinical evidence across multiple neurological indications and regulatory registration. The two compounds address partially overlapping but distinct aspects of neurorestorative pharmacology.

12.4 Actovegin

Composition and mechanism: Actovegin is a deproteinized hemodialysate of calf blood, containing low-molecular-weight peptides, amino acids, nucleosides, and intermediary metabolites of carbohydrate and lipid metabolism [36]. The mechanism of action involves enhancement of cellular glucose uptake and oxygen utilization, antioxidant effects, and anti-inflammatory activity. The compound is registered in several European and Asian countries for cerebrovascular disease, peripheral vascular disease, and diabetic polyneuropathy.

Novelty: Low. The compound is a biological extract with a broadly similar regulatory and scientific profile to Cerebrolysin (complex biological mixture, manufactured by tissue hydrolysis, not approved in major Western jurisdictions).

Effect size: Modest in cerebrovascular indications. The ARTEMIDA trial (randomized, double-blind, placebo-controlled, 503 patients with post-stroke cognitive impairment) demonstrated significant improvement on the Montreal Cognitive Assessment at 6 months compared to placebo [36]. Effect sizes are generally comparable to those reported for Cerebrolysin in similar indications.

Promising potential: Low to moderate. The compound is registered in several jurisdictions but faces similar regulatory challenges to Cerebrolysin in Western markets. The ARTEMIDA trial is the principal large randomized trial.

Side-effect profile: Favorable. Adverse event rates are comparable to placebo in controlled trials. The calf blood derivation raises transmissible spongiform encephalopathy concerns in some regulatory jurisdictions, which has limited market access.

Overall validation: Moderate. The ARTEMIDA trial provides a single large randomized dataset. The overall evidence base is smaller than that of Cerebrolysin.

Comparison to Cerebrolysin: Actovegin and Cerebrolysin occupy similar regulatory and clinical niches as biological mixture products for neurological indications. Cerebrolysin has the advantage of a larger clinical evidence base, more identified neurotrophic mechanisms, and broader registration. Actovegin has the advantage of demonstrated efficacy in diabetic polyneuropathy, an indication for which Cerebrolysin has not been studied. The two compounds are sometimes used concurrently in clinical practice in Eastern European and Asian jurisdictions, although controlled evidence for the combination is absent.

12.5 Semax

Composition and mechanism: Semax is a synthetic heptapeptide (Met-Glu-His-Phe-Pro-Gly-Pro) derived from the N-terminal fragment of adrenocorticotrophic hormone (ACTH 4-10) with an additional C-terminal Pro-Gly-Pro extension that confers protease resistance [37]. The mechanism of action involves activation of melanocortin receptors (MC3R, MC4R), upregulation of BDNF expression, modulation of serotonergic and dopaminergic neurotransmission, and anti-inflammatory effects. The compound is administered intranasally, which distinguishes it from the injectable Cerebrolysin.

Novelty: Moderate. The melanocortin-receptor-mediated neurotrophic mechanism is distinct from the Trk-receptor-mediated mechanism of Cerebrolysin. The intranasal route of administration is a practical advantage.

Effect size: Modest in available clinical data. The compound is registered in Russia for stroke recovery and cognitive enhancement, with clinical evidence from Russian clinical trials demonstrating improvement on cognitive testing batteries

[37]. The evidence base is limited in volume and methodological quality by Western regulatory standards.

Promising potential: Low to moderate. The compound is registered only in Russia and several CIS countries. Broader international clinical development has not been pursued.

Side-effect profile: Favorable. The compound is well tolerated intranasally, with no serious adverse events reported in available clinical data.

Overall validation: Low to moderate. The evidence base is limited to Russian clinical studies and is not accessible to systematic review by international regulatory bodies. The compound serves as a research tool for melanocortin-receptor pharmacology and as a clinical neurotrophic agent in Russia.

Comparison to Cerebrolysin: Semax and Cerebrolysin act through distinct mechanisms (melanocortin receptor activation versus Trk receptor activation by neurotrophic peptide fragments). Semax has the practical advantages of intranasal administration and defined single-peptide composition. Cerebrolysin has the advantages of a larger clinical evidence base, multi-target neurotrophic activity, and broader international registration. The two compounds are used concurrently in Russian clinical practice for stroke recovery, although controlled evidence for the combination is absent.

12.6 Comparator summary

The five comparators occupy distinct positions in the neurotrophic and neuroprotective pharmacology space. **Cortexin** is the most mechanistically similar to Cerebrolysin but has a smaller evidence base and more limited registration. **P21** represents the most rationally designed and mechanistically targeted approach but has no clinical data. **NSI-189** is the most mechanistically novel (small-molecule neurogenesis stimulation) but has mixed Phase 2 results and is not in active development for neurological indications. **Actovegin** occupies a similar regulatory niche with the ARTEMIDA trial as its principal clinical evidence but has a different tissue source and a different mechanistic profile. **Semax** offers the convenience of intranasal administration and a defined single-peptide composition but has an evidence base limited to Russian clinical studies.

Cerebrolysin occupies a unique position in this comparator landscape: it has the largest clinical evidence base among the neurotrophic peptide agents (over 200 clinical studies, including the CASTA and CARS landmark trials), the broadest international registration (over 50 countries), the most extensively characterized multi-target mechanism of action, and the longest clinical track record (over 70 years of clinical use since the original 1949 formulation). Its principal limitations are the absence of approval in major Western regulatory jurisdictions, the heterogeneity of the clinical trial quality, the complexity of the biological mixture product that complicates regulatory characterization, and the negative primary endpoint result of the CASTA trial that tempers the stroke evidence base.

The practical positioning of Cerebrolysin relative to the comparators depends on the clinical or research context. For acute stroke recovery with structured rehabilitation, the CARS trial evidence positions Cerebrolysin as the most supported neurotrophic adjunct. For Alzheimer's disease, the meta-analytic evidence positions Cerebrolysin as an add-on to standard cholinesterase inhibitor therapy with modest but statistically significant cognitive benefit. For traumatic brain injury, the accumulated evidence from 27 clinical studies positions Cerebrolysin as the most extensively studied neurotrophic agent in this indication. For research applications requiring mechanistic specificity, P21 or NSI-189 may be more informative owing to their defined mechanisms, but Cerebrolysin provides the broadest neurotrophic coverage for multimodal neuroprotection studies.

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