

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cortexin

A heterogeneous low-molecular-weight neuropeptide preparation extracted from the cerebral cortex of young cattle and pigs, registered in the Russian Federation as a neuroprotective agent for cerebrovascular disorders, traumatic brain injury, cognitive impairment, and perinatal central nervous system lesions, distinguished from Cerebrolysin by cortex-specific sourcing and intramuscular administration.

DOCUMENT	KDC-MN-1505
ISSUED	2026-05-15
REVISION	1.0
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COMPOUND CLASS	Polypeptide bioregulator complex derived from cerebral cortex with neurotrophic, neuroprotective, and nootropic activity

ABSTRACT

Cortexin is a lyophilized complex of water-soluble polypeptide fractions with molecular weights ranging from 1,000 to 10,000 Daltons, obtained by acetic acid extraction from the cerebral cortex of cattle and pigs younger than 12 months of age. The preparation contains predominantly acidic and neutral polypeptides (70 to 95 percent of total mass), free amino acids (including glutamic acid, aspartic acid, glycine, serine, lysine, and alanine as quantitatively predominant species), and trace quantities of vitamins, minerals, and fatty acids. Unlike single-sequence peptide therapeutics, Cortexin is a heterogeneous mixture without a defined primary structure, and its pharmacological activity is attributed to the collective action of multiple bioactive peptide fractions rather than to any single molecular entity.

The compound was developed within the Soviet and subsequently Russian bioregulator research program led by Vladimir Khavinson at the Saint Petersburg Institute of Bioregulation and Gerontology beginning in the 1980s, with the first clinical applications in military and aerospace medicine. Cortexin received pharmaceutical registration in the Russian Federation in 1999 and is manufactured by GEROPHARM LLC (Saint Petersburg) as a lyophilisate for intramuscular injection at 5 mg and 10 mg strengths, with glycine (12 mg) as the stabilizing excipient. The compound is registered in Russia, Ukraine, Kazakhstan, Belarus, Uzbekistan, and several other Commonwealth of Independent States jurisdictions for the treatment of acute and chronic cerebrovascular disorders, traumatic brain injury, cognitive

impairment, encephalopathy of various origins, epilepsy as adjunctive therapy, and perinatal central nervous system lesions in children. It is not registered or approved in the European Union, the United States, Japan, or any jurisdiction with International Council for Harmonisation regulatory standards.

The molecular mechanisms of Cortexin are pleiotropic and incompletely characterized at the individual peptide level. Demonstrated activities include modulation of glutamatergic transmission through interaction with AMPA receptors, kainate receptors, and metabotropic glutamate receptors (mGluR1 and mGluR5); GABAergic modulation through GABA-A receptor binding; activation of neurotrophic signaling cascades including brain-derived neurotrophic factor and nerve growth factor pathways; antioxidant activity through restoration of pro-oxidant and antioxidant system balance; anti-inflammatory action at both cerebral and systemic levels; and anti-apoptotic effects on neurons under ischemic and excitotoxic stress. Radioactively labeled Cortexin peptides have been demonstrated to cross the blood-brain barrier in mice, supporting direct central nervous system activity. Neuron-specific proteins including beta-5-tubulin, creatine kinase B, and protein 14-3-3 alpha/beta have been identified as molecular partners of Cortexin peptides in brain tissue.

The clinical evidence base for Cortexin is substantial within the Russian-language medical literature but limited in the international peer-reviewed literature. The largest body of evidence supports efficacy in acute ischemic stroke, where Cortexin at 10 mg twice daily intramuscularly for 10 days is included in Russian national clinical practice guidelines. A multicenter randomized controlled study (Fedin et al. 2018)

demonstrated dose-dependent effects of Cortexin (10 mg versus 20 mg versus standard care alone) on neurological deficit severity, asthenia, and sleep disturbance in patients with chronic cerebral ischemia, with antioxidant effects confirmed by laboratory markers regardless of dose. A multicenter study of cognitive dysfunction in children demonstrated improvement in attention, visual memory, and thinking in pediatric patients with consequences of perinatal central nervous system lesions. In cerebral palsy with comorbid epilepsy, Cortexin as adjunctive therapy reduced seizure frequency by more than two-fold in 36.9 percent of patients while improving motor function. Comparative preclinical studies have demonstrated neuroprotective efficacy comparable to Cerebrolysin and superior to Actovegin in rat models of acute and chronic brain ischemia. A systematic review of animal-derived nootropics noted that the limited number of eligible Cortexin studies precluded meta-analysis, though available data suggested potential efficacy with no safety concerns. The compound is generally well tolerated; the principal adverse events are injection site reactions (8 to 15 percent), headache (5 to 12 percent), dizziness (3 to 8 percent), and rare hypersensitivity reactions including anaphylaxis. This monograph reviews the composition, extraction methodology, and physicochemical properties of Cortexin; the pleiotropic molecular pharmacology; the pharmacokinetic limitations inherent to a heterogeneous peptide preparation; the clinical evidence base across cerebrovascular, traumatic, cognitive, and pediatric indications; sourcing and quality verification considerations; reconstitution and handling protocols; stack-interaction implications; adverse-event signal; and a structured comparative assessment of five neuroprotective alternatives against Cortexin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: None assigned. Cortexin is classified as a complex biological preparation and has not received an International Nonproprietary Name from the World Health Organization.

Marketed name: Cortexin (GEROPHARM LLC, Saint Petersburg, Russian Federation). The compound is sold under this single brand name across all registered jurisdictions.

Development origin: The compound was developed at the Saint Petersburg Institute of Bioregulation and Gerontology (formerly the Military Medical Academy bioregulation laboratory) under the direction of Vladimir Khavinson. No formal development code comparable to pharmaceutical industry convention was assigned; the compound is identified in the literature by the trade name Cortexin or by the generic descriptor "polypeptide fractions of cerebral cortex."

Chemical Abstracts Service registry number: None assigned. Because Cortexin is a heterogeneous polypeptide mixture rather than a single chemical entity, it does not carry a CAS registry number. Individual peptide fractions within the mixture have not been individually isolated and registered.

Anatomical Therapeutic Chemical classification: Not assigned by the World Health Organization Collaborating Centre. In the Russian pharmaceutical register, Cortexin is classified under nootropic agents and neuroprotective agents (N06BX in approximate ATC equivalence).

1.2 Structural class and chemistry

Cortexin is a heterogeneous complex of water-soluble polypeptide fractions extracted from the cerebral cortex of cattle (*Bos taurus*) and pigs (*Sus scrofa domestica*) younger than 12 months of age. The structural class places it within the family of tissue-derived peptide bioregulators, a group of preparations that also includes

Cerebrolysin (whole porcine brain hydrolysate), Retinalamin (retinal peptide extract), Thymalin (thymus peptide extract), and Epithalon (synthetic tetrapeptide bioregulator) [1, 2].

Molecular weight range: Individual polypeptide components range from approximately 1,000 to 10,000 Daltons. The preparation is enriched for the low-molecular-weight fraction by ultrafiltration during manufacturing, excluding proteins and peptide fragments above 10,000 Daltons [3].

Isoelectric point distribution: The polypeptide fractions have isoelectric points distributed across the range of pI 3.5 to 9.5, with a predominance (70 to 95 percent) of acidic and neutral species [3].

Amino acid composition (per milligram of lyophilisate): Glutamic acid, 581 nmol; aspartic acid, 446 nmol; isoleucine, 356 nmol; glycine, 298 nmol; serine, 268 nmol; lysine, 253 nmol; alanine, 246 nmol; threonine, 212 nmol; arginine, 202 nmol; proline, 187 nmol; phenylalanine, 162 nmol; histidine, 116 nmol; tyrosine, 109 nmol. The amino acid profile reflects the cortical tissue origin and is enriched in excitatory (glutamic acid, aspartic acid) and inhibitory (glycine) neurotransmitter amino acids [4].

Excipient: Glycine, 12 mg per vial, serves as a lyoprotective stabilizer.

Physical properties: White to off-white lyophilized powder or porous mass. Freely soluble in water and in physiological saline upon reconstitution. The reconstituted solution is clear to slightly opalescent with a pH of approximately 5.0 to 7.5.

1.3 Extraction and manufacturing

The manufacturing process for Cortexin involves several principal stages: harvesting of cerebral cortex tissue from cattle and pigs younger than 12 months of age under veterinary sanitary control; homogenization of cortical tissue in cold acetic acid (0.1 to 1.0 M) to extract water-soluble peptides and to inactivate proteases; sequential ultrafiltration through molecular weight cutoff membranes (10 kDa nominal) to remove high-molecular-weight proteins, prions, and potential immunogens; purification by ion-exchange chromatography to enrich the bioactive peptide fraction; addition of glycine as a lyoprotective agent; sterile filtration; filling into glass vials; and lyophilization under controlled conditions [3, 5].

Quality control at the manufacturing level includes characterization of the peptide profile by reverse-phase high-performance liquid chromatography, amino acid analysis by ion-exchange chromatography with post-column ninhydrin derivatization, endotoxin testing by Limulus amoebocyte lysate assay, sterility testing, residual moisture determination, and batch-to-batch reproducibility assessment by peptide fingerprinting. GEROPHARM has published batch consistency data indicating that the HPLC peptide fingerprint is reproducible within defined acceptance criteria across production lots, though the specific acceptance limits are proprietary [5].

The cortex-specific sourcing is the principal compositional distinction from Cerebrolysin, which is derived from whole porcine brain (including subcortical structures, brainstem, and cerebellum) and is processed by enzymatic hydrolysis rather than acid extraction. The cortex-specific extraction of Cortexin is hypothesized to enrich for cortically expressed neuropeptides, neurotrophic factors, and signaling peptides that may confer tissue-specific activity on cerebral cortex neurons, though this hypothesis has not been conclusively demonstrated by comparative peptide profiling [6].

2. Abstract

Cortexin is a polypeptide bioregulator complex derived from the cerebral cortex of young cattle and pigs, registered in the Russian Federation and several Commonwealth of Independent States jurisdictions as a neuroprotective agent for cerebrovascular disorders, traumatic brain injury, cognitive impairment, encephalopathy, epilepsy (adjunctive), and perinatal central nervous system lesions. The preparation contains heterogeneous water-soluble polypeptide fractions (molecular weight 1,000 to 10,000 Daltons) that cross the blood-brain barrier and exert pleiotropic neurotrophic, neuroprotective, antioxidant, anti-inflammatory, and anti-apoptotic effects through interactions with glutamatergic, GABAergic, and neurotrophic signaling systems [3, 7].

The compound occupies a distinctive position within the class of tissue-derived neuropeptide preparations. Unlike Cerebrolysin, which is derived from whole porcine brain and administered intravenously, Cortexin is sourced specifically from cerebral cortex tissue and administered intramuscularly. Unlike synthetic nootropics such as piracetam or citicoline, Cortexin is a biological preparation with inherent batch variability and a pharmacological profile that reflects the collective activity of multiple bioactive peptides rather than a single defined mechanism [6].

The clinical evidence base is substantial within the Russian medical literature, encompassing multicenter randomized controlled trials in chronic cerebral ischemia [8], open clinical trials in acute ischemic stroke [9], multicenter observational studies of cognitive impairment in chronic cerebrovascular pathology [10], pediatric trials in cerebral palsy with epilepsy [11], and studies in perinatal central nervous system lesions [12]. The international evidence base is limited, and the compound has not been evaluated in trials meeting International Council for Harmonisation Good Clinical Practice standards for regulatory submission in the European Union, the United States, or Japan. A systematic review and meta-analysis of animal-derived nootropics concluded that available Cortexin data suggested potential efficacy with no safety concerns, but that the limited number of eligible studies precluded formal meta-analysis [13].

The compound is administered at 10 mg intramuscularly once or twice daily for courses of 10 days, with repeat courses after intervals of 10 days to 6 months depending on indication. Pediatric doses range from 0.5 mg/kg in neonates to 5 to 10 mg in older children. The safety profile is favorable; the principal adverse events are injection site reactions, headache, and dizziness, with rare hypersensitivity reactions. The compound has no characterized drug-drug interactions through cytochrome P450 pathways owing to its peptide composition and is not subject to hepatic oxidative metabolism.

3. Discovery and Development History

3.1 Origin in Soviet bioregulator research

The development of Cortexin is rooted in the Soviet bioregulation research program initiated in 1973 at the Military Medical Academy in Leningrad (now Saint Petersburg). The program was commissioned by the Soviet Ministry of Defense to address the problem of premature physiological aging observed in submarine crews, missile silo operators, and cosmonauts exposed to chronic environmental stressors including radiation, confinement, and extremes of temperature and pressure [1, 14]. The research team, led by Vladimir Khavinson and subsequently institutionalized at the Saint Petersburg Institute of Bioregulation and Gerontology, hypothesized that low-molecular-weight peptide fractions extracted from specific organs could restore homeostatic function in the corresponding target tissues through a mechanism termed "peptide bioregulation" [1].

Between 1973 and 2000, Khavinson and colleagues extracted over 20 complexes of physiologically active peptides from various organs and synthesized 15 additional short peptides (di-, tri-, and tetrapeptides) as candidate bioregulators. Six of these preparations achieved pharmaceutical registration in the Russian Federation: Thymalin (thymus extract, registered 1982), Prostatilen (prostate extract), Retinalamin (retinal extract), Cortexin (cerebral cortex extract, registered 1999), Epithalon (synthetic tetrapeptide), and others [1, 14]. Cortexin was specifically developed as a cerebral cortex-targeted bioregulator for neuroprotection and cognitive support.

3.2 Pharmaceutical registration

Cortexin received pharmaceutical registration in the Russian Federation in 1999 under registration certificate number P N000514/01. The initial approved indications were acute and chronic cerebrovascular disorders, traumatic brain injury, and cognitive impairment of various origins. Subsequent label expansions added epilepsy (as adjunctive therapy), encephalopathy, and perinatal central nervous system lesions in children [5].

The manufacturer is GEROPHARM LLC (Saint Petersburg), which produces the preparation at a GMP-certified facility. The product is supplied as a lyophilisate for preparation of solution for intramuscular injection in glass vials containing 5 mg or 10 mg of polypeptide fractions with 12 mg of glycine as excipient [5].

3.3 Expansion of the clinical research literature

The Russian-language clinical literature on Cortexin expanded substantially between 2000 and 2020. Over 200 clinical publications have been indexed in the Russian biomedical literature databases (eLibrary.ru, CyberLeninka), covering applications in adult and pediatric neurology, neurosurgery, and rehabilitation medicine. The principal research centers include the Russian Military Medical Academy (Saint Petersburg), the Research Center of Neurology (Moscow), the Burdenko National Medical Research Center of Neurosurgery (Moscow), and multiple regional neurological centers across the Russian Federation [5, 15].

The compound was included in the Russian national clinical practice guidelines for the management of acute ischemic stroke, where it is recommended at a dose of 10 mg twice daily (morning and afternoon) intramuscularly for 10 days, with a second course after a 10-day interval [9]. This guideline inclusion, while significant within the Russian clinical system, does not carry equivalence to guideline recommendations in systems that require International Council for Harmonisation standard evidence.

3.4 International recognition and limitations

International awareness of Cortexin has remained limited outside the Russian-speaking scientific community. The compound has been the subject of a small number of English-language publications, principally comparative preclinical studies published in PLoS ONE and other international journals [6, 16]. The primary barrier to international recognition is the absence of clinical trials conducted under International Council for Harmonisation Good Clinical Practice standards with regulatory-grade documentation, independent data monitoring, and pre-registered protocols in international registries. The Russian-language evidence base, while quantitatively substantial, has been characterized by systematic reviewers as having moderate to high risk of bias, with limited blinding, inconsistent outcome measures, and absence of independent data monitoring committees [13].

4. Molecular Pharmacology

Cortexin is a multi-component preparation with pleiotropic pharmacological activity. Because the compound is a heterogeneous peptide mixture rather than a single molecular entity, the mechanism of action cannot be reduced to a single receptor-ligand interaction. Instead, the pharmacology reflects the collective activity of multiple peptide fractions acting on multiple molecular targets within the central nervous system. The principal characterized mechanisms are described below.

4.1 Glutamatergic modulation

In vitro receptor binding and functional assays have demonstrated that Cortexin peptide fractions interact with multiple glutamate receptor subtypes. High-affinity interactions have been reported with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, kainate receptors, and metabotropic glutamate receptors mGluR1 and mGluR5 [7, 17]. The functional consequence is modulation of excitatory neurotransmission, with the net effect described as normalization of the glutamate-GABA balance rather than simple agonism or antagonism at any single receptor subtype.

The normalization of glutamatergic transmission is proposed as a principal mechanism underlying the neuroprotective activity in ischemic conditions, where glutamate excitotoxicity is a major driver of neuronal death. By reducing excessive glutamatergic activation during the acute phase of ischemia while preserving physiological glutamate signaling during recovery, Cortexin may limit excitotoxic injury without the cognitive impairment associated with blanket glutamate receptor antagonism [7].

4.2 GABAergic modulation

Cortexin peptide fractions demonstrate binding affinity for GABA-A receptors, with the observed in vivo effects consistent with a mild GABAergic facilitating action [7, 17]. The GABAergic component of the mechanism is proposed to contribute to the anticonvulsant activity observed in pediatric epilepsy studies and to the anxiolytic effects reported in chronic cerebral ischemia trials [8, 11].

4.3 Neurotrophic factor activation

Cortexin administration in animal models has been associated with increased expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in cortical and hippocampal tissue [7, 18]. The neurotrophic activation is proposed as the molecular basis for the long-term cognitive improvement observed in clinical studies, where benefit persists beyond the 10-day treatment course and is augmented by repeated courses [8].

The downstream signaling consequences of neurotrophic factor activation include ERK1/2 mitogen-activated protein kinase pathway engagement, phosphoinositide 3-kinase/Akt survival signaling, and cyclic AMP response element binding protein (CREB) transcriptional activation, all of which promote neuronal survival, synaptic plasticity, and axonal regeneration [7].

4.4 Antioxidant activity

Cortexin has demonstrated antioxidant effects both in vitro and in vivo. In a model of accelerated aging in rats, Cortexin restored the balance between pro-oxidant and antioxidant systems, reducing markers of lipid peroxidation (malondialdehyde) and increasing the activity of endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) [7, 19]. The multicenter randomized controlled study of Fedin et al. (2018) confirmed antioxidant effects in human patients with chronic cerebral ischemia by laboratory biomarkers, regardless of the Cortexin dose (10 mg or 20 mg) [8].

4.5 Anti-inflammatory activity

Anti-inflammatory action has been demonstrated at both the cerebral and systemic levels. Cortexin reduces the expression of pro-inflammatory cytokines including tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6, and modulates the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which integrates antioxidant and anti-inflammatory responses [7, 17]. The anti-inflammatory mechanism is proposed to contribute to neuroprotection in post-ischemic neuroinflammation and in traumatic brain injury, where secondary inflammatory cascades amplify the initial mechanical or ischemic insult.

4.6 Anti-apoptotic effects

Cortexin peptide fractions have been shown to inhibit apoptotic pathways in neurons under ischemic and excitotoxic stress. The anti-apoptotic mechanism involves modulation of the Bcl-2/Bax ratio (favoring the anti-apoptotic Bcl-2), reduction of cytochrome c release from mitochondria, and decreased activation of caspase-3 [7, 17]. Histological examination in animal models of cerebral ischemia confirmed that Cortexin treatment decreased neuronal damage and preserved a higher proportion of morphologically normal neurons compared with untreated controls [6].

4.7 Molecular partners and target identification

Proteomics-based target identification studies have identified three neuron-specific proteins as molecular partners of Cortexin peptides in brain tissue: beta-5-tubulin (a neuronal cytoskeletal protein involved in axonal transport and synaptic integrity), creatine kinase B (the brain-type isoenzyme of creatine kinase, critical for neuronal energy metabolism), and protein 14-3-3 alpha/beta (a scaffolding protein involved in signal transduction, apoptosis regulation, and neurotransmitter synthesis) [17]. The identification of these molecular partners provides a mechanistic framework for understanding the cytoskeletal stabilization, energy metabolism support, and signal transduction modulation that characterize the compound's neuroprotective profile.

4.8 Blood-brain barrier penetration

Biodistribution studies using radioactively labeled Cortexin in mice have demonstrated that the polypeptide fractions cross the blood-brain barrier and distribute into brain tissue [6, 7]. The low molecular weight of the constituent peptides (below 10,000 Daltons) facilitates transcytosis or passive diffusion across the cerebrovascular endothelium. The demonstration of central nervous system penetration is critical to the pharmacological rationale, as the proposed mechanisms of action require direct interaction of peptide fractions with neuronal and glial targets in the brain parenchyma.

5. Pharmacokinetics

5.1 General pharmacokinetic considerations

The pharmacokinetics of Cortexin are inherently difficult to characterize by conventional methods because the preparation is a heterogeneous mixture of peptides rather than a single molecular entity. Standard pharmacokinetic parameters (bioavailability, volume of distribution, clearance, half-life) have not been determined for the complete preparation, and individual peptide fractions have not been isolated and characterized pharmacokinetically. The following pharmacokinetic description is based on the general pharmacological behavior of low-molecular-weight peptides and on the limited specific studies available for Cortexin [3, 7].

5.2 Absorption

Cortexin is administered by intramuscular injection, bypassing gastrointestinal absorption. Intramuscular administration provides relatively rapid absorption of low-molecular-weight peptides into the systemic circulation, with expected peak plasma concentrations within 15 to 60 minutes of injection depending on injection site vascularity, injection volume, and individual variation in muscle blood flow [3].

Oral administration is not feasible because the peptide fractions would be degraded by gastrointestinal proteases (pepsin, trypsin, chymotrypsin) before significant absorption could occur. Subcutaneous administration has been used in some research contexts but is not the registered route. Rectal administration (suppository formulation) has been studied for pediatric applications and shows evidence of systemic absorption, though bioavailability data relative to intramuscular administration are not published [20].

5.3 Distribution

The low molecular weight of the constituent peptides (1,000 to 10,000 Daltons) and demonstrated blood-brain barrier penetration indicate substantial distribution into the central nervous system. Volume of distribution has not been formally deter-

mined. Plasma protein binding characteristics are unknown for the individual peptide components. Based on general peptide pharmacology, extensive tissue distribution with limited plasma protein binding is expected [7].

5.4 Metabolism and elimination

Low-molecular-weight peptides are generally metabolized by ubiquitous tissue peptidases (aminopeptidases, carboxypeptidases, endopeptidases) to their constituent amino acids, which are then incorporated into normal amino acid metabolism pools. The half-life of individual low-molecular-weight peptides in the systemic circulation is typically minutes to hours, necessitating daily dosing for sustained pharmacological effect [3].

Cortexin is not metabolized by cytochrome P450 enzymes and does not undergo hepatic oxidative metabolism. It is therefore not subject to the CYP-mediated drug-drug interactions that characterize small-molecule pharmacotherapy. Elimination is through peptidase-mediated degradation followed by renal excretion of amino acid metabolites and small peptide fragments.

5.5 Routes of administration

The registered route is intramuscular injection. The lyophilisate is reconstituted with 1 to 2 mL of water for injection or 0.5 percent procaine (lidocaine) solution immediately before administration. The reconstituted solution is injected into the deltoid or gluteal muscle. Administration should occur in the morning or early afternoon; evening administration is generally avoided due to reported psychoactivating effects that may interfere with sleep [5].

5.6 Special populations

Pediatric: Cortexin is approved for pediatric use in Russia from the neonatal period onward. Neonatal dosing is 0.5 mg/kg intramuscularly for 10 days; pediatric dosing for children over 20 kg body weight is 10 mg intramuscularly daily for 10 days [5, 12]. The compound has been studied in premature neonates (33 to 35 weeks gestational age) with perinatal hypoxia, with improvement in general condition and decreased severity of neurological disorders reported in 59.1 percent of treated infants [12].

Geriatric: Geriatric pharmacokinetics have not been separately characterized. The compound is used in elderly populations for chronic cerebral ischemia and cognitive impairment without dose adjustment in the Russian prescribing information [8, 10].

Hepatic impairment: Because the compound is not hepatically metabolized through cytochrome P450 pathways, hepatic impairment is not expected to substantially alter the pharmacokinetic profile.

Renal impairment: Severe renal impairment may delay elimination of amino acid metabolites, but this is not expected to produce clinically significant accumulation given the small peptide doses involved. No dose adjustment is recommended in the Russian prescribing information.

6. Preclinical Pharmacology

6.1 Neuroprotection in acute cerebral ischemia

The most rigorous preclinical evaluation of Cortexin was published by Gulyaev et al. (2021) in PLoS ONE, the first study to directly compare the neuroprotective activity of Cortexin, Cerebrolysin, and Actovegin in standardized rat models of acute and chronic brain ischemia [6]. In the acute model (middle cerebral artery occlusion), Cortexin at 1 mg/kg and 3 mg/kg demonstrated neuroprotective efficacy comparable to Cerebrolysin at 538 mg/kg and 1614 mg/kg, as measured by infarct volume reduction, neurological deficit scoring, and histological preservation of neurons. Actovegin was inferior to both Cortexin and Cerebrolysin. The substantially lower effective dose of Cortexin relative to Cerebrolysin (approximately 500-fold by weight) is consistent with a higher potency preparation, likely reflecting the cortex-specific enrichment and the acid extraction methodology.

6.2 Neuroprotection in chronic cerebral ischemia

In the chronic model (bilateral common carotid artery stenosis), Cortexin and Cerebrolysin produced comparable improvements in cognitive function as assessed by Morris water maze and novel object recognition, and in hippocampal neuron preservation as assessed by histological examination [6]. Actovegin effects were less pronounced in the chronic model as well. The chronic ischemia data support a sustained neuroprotective and neurotrophic mechanism beyond the acute anti-excitotoxic and anti-apoptotic effects.

6.3 Comparative behavioral pharmacology

A comparative behavioral study by Shabanov et al. (2007) examined the effects of Cortexin and Cerebrolysin injected directly into brain ventricles in rats [24]. When administered by this central route (bypassing peripheral pharmacokinetics), Cortexin produced more pronounced psychoactivating effects across all behavioral tests compared with Cerebrolysin, consistent with higher cortex-specific bioactiv-

ity of the cortex-derived preparation. The intraventricular administration route confirmed that the behavioral effects are centrally mediated rather than secondary to peripheral mechanisms.

6.4 Developmental neuropharmacology

A 2025 study in Biomedicines (Zueva et al. 2025) evaluated the neurotropic effects of Cortexin in rodent models of mental and physical developmental delay [20]. Cortexin administered as intramuscular solution or rectal suppositories produced pronounced neurotropic effects on developmental milestones and behavioral outcomes in neonatal rats, supporting the pediatric indication for perinatal central nervous system lesions.

6.5 Memory and hippocampal protection in chronic ischemia

A comparative study of the protective effects of Cortexin, Cerebrolysin, and Actovegin on memory impairment and hippocampal morphology in rats with chronic brain ischemia (Koroleva et al. 2020) demonstrated that Cortexin preserved hippocampal CA1 pyramidal neuron density and spatial memory performance in the Morris water maze, with efficacy comparable to Cerebrolysin and superior to Actovegin [21].

6.6 Antioxidant effects in aging models

Cortexin administered to rats in a model of accelerated aging (Kozina et al. 2012) restored the ratio of pro-oxidant and antioxidant systems, reducing malondialdehyde levels and increasing superoxide dismutase and catalase activity in both brain tissue and peripheral blood [19]. The dual central and peripheral antioxidant action was observed at clinically relevant doses, supporting the proposed antioxidant mechanism in human patients.

7. Clinical Evidence Base

7.1 Acute ischemic stroke

The largest body of clinical evidence for Cortexin supports its use in acute ischemic stroke. Cortexin is included in Russian national clinical practice guidelines for the management of acute ischemic stroke at a dose of 10 mg twice daily (morning and afternoon) intramuscularly for 10 days, with a second course after a 10-day interval [9].

An open clinical trial of Cortexin in 272 patients with acute ischemic stroke (Skoromets et al. 2008) evaluated the addition of Cortexin (10 mg intramuscularly daily for 10 days) to standard stroke care [9]. The Cortexin group demonstrated statistically significant improvement in neurological deficit scores (National Institutes of Health Stroke Scale), functional recovery (Barthel Index), and cognitive performance compared with the standard care control group at day 11 and at day 30 follow-up.

An evaluation of Cortexin in the complex rehabilitation of early verticalization in acute ischemic stroke (Baturin et al. 2019) demonstrated that addition of Cortexin to a rehabilitation protocol incorporating early mobilization improved neurological outcomes and was well tolerated, with no patients experiencing adverse drug interactions with concurrent antihypertensive, antiplatelet, or statin therapy [22].

A prospective, double-blinded comparative study published in the Journal of the Neurological Sciences (Verclytte et al. 2019) assessed the pharmacological activity of Cerebrolysin and distinct peptide preparations (including Cortexin) for the treatment of embolic stroke [16]. Among all tested neuropeptide preparations, Cerebrolysin was the only agent associated with a significant improvement in neurological outcome compared with saline, while Cortexin did not achieve significance in this international comparison study. This result highlights the discrepancy between the Russian-language evidence (generally positive) and the international evidence (mixed) for Cortexin in stroke.

7.2 Chronic cerebral ischemia

The multicenter randomized controlled study by Fedin et al. (2018) is the most rigorous published trial of Cortexin in chronic cerebral ischemia [8]. The study enrolled patients across multiple Russian centers and randomized them to three groups: intramuscular injection of 20 mg of Cortexin daily for 10 days, 10 mg of Cortexin daily for 10 days, or standard treatment alone. The treatment course was repeated after 6 months.

The study demonstrated a dose-dependent effect of Cortexin on the severity of neurological disorders, asthenia, and sleep disturbance. The 20 mg dose produced greater improvement in neurological deficit scores than the 10 mg dose, which in turn was superior to standard treatment alone. Antidepressant and anxiolytic effects were observed principally after repeated courses rather than after a single course. Laboratory markers confirmed antioxidant effects regardless of the Cortexin dose. The safety and tolerability of both doses were confirmed, with no serious adverse events attributed to the study drug [8].

A multicenter observation study of Cortexin and citicoline (recoglan) in the treatment of cognitive impairment in chronic cerebrovascular pathology (Chukanova et al. 2019) compared the two agents in patients with established chronic cerebral ischemia and demonstrated improvements in cognitive test performance with both agents, with Cortexin showing advantages in certain cognitive domains [10].

7.3 Cognitive impairment in adults

The combination of Cortexin and memantine for cognitive impairment in chronic cerebral ischemia has been studied in clinical trials. The rationale for the combination is complementary mechanism: Cortexin provides neurotrophic and neuroprotective support while memantine provides NMDA receptor antagonism that limits excitotoxicity. Published data suggest additive benefit of the combination compared with either agent alone, though the studies were conducted in Russian clinical settings without international trial registration [23].

7.4 Pediatric indications

Cognitive dysfunction in children: A multicenter study of the efficacy of Cortexin in the treatment of cognitive dysfunction in children with consequences of perinatal central nervous system lesions demonstrated significant improvement in attention, visual memory, and thinking in the treated group. The study reported good tolerability and supported the use of Cortexin as a beneficial therapy for children with attention deficit hyperactivity disorder, speech delay, and perinatal central nervous system damage [12, 25].

Cerebral palsy with epilepsy: A clinical trial in 84 pediatric patients (ages 1 to 11 years) with cerebral palsy combined with epilepsy evaluated Cortexin at 5 to 10 mg intramuscularly (adjusted for age and body weight) as adjunctive therapy to antiepileptic drugs [11]. Cortexin plus antiepileptic drugs reduced seizure frequency by more than two-fold in 31 patients (36.9 percent), with concurrent improvement in motor function. An additional 15 patients (17.8 percent) showed improvement in motor function without significant seizure reduction, and 14 patients (16.7 percent) showed seizure frequency reduction without significant motor improvement. Aggravation of epileptic seizures was observed in only 1 patient with West syndrome (1.2 percent), a rate significantly lower than the probability of seizure aggravation attributed to antiepileptic drug therapy alone [11].

Perinatal central nervous system lesions: Cortexin at 0.5 mg/kg during the first 10 days of life has been administered to premature neonates (33 to 35 weeks gestational age) whose intrauterine development proceeded under conditions of chronic hypoxia. Improvement in general condition and decreased severity of neurological disorders was reported in 59.1 percent of treated infants [12].

7.5 Traumatic brain injury

Cortexin is included in the Russian prescribing information for traumatic brain injury, and clinical use in this indication is established in Russian neurological practice. Published clinical data in traumatic brain injury are principally from observational studies and case series rather than from randomized controlled trials. The proposed mechanism in traumatic brain injury is the composite neuroprotective, anti-inflammatory, and neurotrophic activity that limits secondary injury cascades and promotes neuronal recovery [15].

7.6 Comparative efficacy in ischemic stroke

A comparative analysis of the efficacy of certain neuroprotectors in ischemic stroke (Rumyantseva et al. 2008) compared Cortexin with Cerebrolysin and other neuroprotective agents in patients with moderate ischemic stroke [26]. The study reported that Cortexin exerted a similar and marked effect to Cerebrolysin, with some advantages regarding the absence of side effects and cost-effectiveness. This finding is consistent with the preclinical comparison demonstrating comparable neuroprotective efficacy between the two preparations [6].

8. Sourcing and Quality Verification

Pharmaceutical-grade Cortexin is manufactured exclusively by GEROPHARM LLC (Saint Petersburg, Russian Federation) and is supplied as a lyophilisate for intramuscular injection in glass vials containing 5 mg or 10 mg of active polypeptide fractions. The pharmaceutical-grade material is the only formulation with regulatory approval in any jurisdiction and is the recommended source for research applications where comparability to clinical material is important [5].

Cortexin is available through Russian pharmaceutical distribution channels and through international pharmacies specializing in Russian-registered pharmaceuticals. Pricing is moderate by Russian pharmaceutical standards (approximately 1,000 to 2,000 Russian rubles per package of 10 vials at the time of monograph preparation). The compound is not scheduled as a controlled substance in any known jurisdiction.

Research-grade Cortexin (bulk polypeptide fractions) is not widely available from standard Western chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress). Some specialty suppliers of Russian bioregulator peptides offer the pharmaceutical-grade product for research use.

Investigators should confirm compound authenticity and quality on every lot through:

- Visual inspection of the lyophilisate (white to off-white powder or porous mass, absence of discoloration or particulate matter)
- Verification of the manufacturer hologram and batch number on the product packaging
- HPLC peptide fingerprint analysis, compared against a reference lot if available
- Amino acid analysis to confirm the expected amino acid composition profile
- Endotoxin testing (Limulus amoebocyte lysate) to confirm absence of bacterial contamination
- Sterility testing for any lot intended for parenteral research use

Because Cortixin is a biological preparation derived from animal tissue, concerns regarding transmissible spongiform encephalopathy (TSE) prion contamination apply. The manufacturer states that source animals are from TSE-free herds under veterinary surveillance and that the manufacturing process includes steps validated for prion inactivation (acid extraction, ultrafiltration). Investigators should request documentation of TSE risk mitigation from the manufacturer or supplier [5].

Third-party analytical verification is challenging for Cortixin because the compound is a heterogeneous mixture rather than a single entity; standard identity confirmation by mass spectrometry of a single molecular ion is not applicable. Peptide fingerprinting by HPLC with comparison to authenticated reference material is the most practical quality confirmation method.

9. Reconstitution and Handling

Cortexin lyophilisate is reconstituted immediately before use by addition of 1 to 2 mL of water for injection or 0.5 percent procaine (novocaine) solution directly into the vial [5]. The procaine formulation reduces injection site pain and is preferred in clinical practice, particularly for repeated courses. Lidocaine 0.5 percent may be substituted for procaine where procaine is unavailable. The reconstituted solution should be clear to slightly opalescent; solutions that are turbid, discolored, or contain visible particulate matter should be discarded.

The reconstituted solution should be administered immediately and should not be stored. The lyophilized powder in the sealed vial should be stored at 2 to 8 degrees Celsius (refrigerated) and protected from light. The shelf life of the intact sealed product is 3 years from the date of manufacture when stored under recommended conditions [5].

The injection is administered into the deltoid or gluteal muscle using standard intramuscular injection technique. The injection should be given slowly over 30 to 60 seconds to minimize local tissue reaction. Administration in the morning or early afternoon is recommended; evening administration should be avoided due to the psychoactivating properties of the compound, which may cause sleep disturbance if administered late in the day [5].

For research applications requiring aliquoting of reconstituted solution, investigators should note that the peptide fractions are susceptible to degradation by adsorption to plastic surfaces and by freeze-thaw cycling. Glass vials or low-binding polypropylene tubes should be used for any storage of reconstituted material. Stability of reconstituted material beyond immediate use has not been formally characterized by the manufacturer and should not be assumed.

10. Stack Interaction Considerations

Cortexin is a peptide preparation that is not metabolized through cytochrome P450 pathways and is not subject to conventional hepatic drug-drug interactions. The following interaction considerations apply to investigators conducting research with Cortexin in combination with other pharmacological agents.

Antiepileptic drugs: Cortexin is approved as adjunctive therapy in epilepsy and has been studied in combination with valproic acid, carbamazepine, lamotrigine, levetiracetam, and topiramate. No adverse pharmacokinetic or pharmacodynamic interactions were reported in the pediatric cerebral palsy trial [11]. The GABAergic facilitating effect of Cortexin may produce additive anticonvulsant activity with GABAergic antiepileptic drugs (valproic acid, benzodiazepines, phenobarbital).

Antihypertensive agents: No adverse interactions with antihypertensive agents (including ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and beta-blockers) were reported in clinical studies [22].

Antiplatelet and anticoagulant agents: Cortexin has been used concurrently with aspirin, clopidogrel, and warfarin in stroke patients without reported interaction [9, 22].

Statins: No adverse interactions with statin therapy have been reported in clinical studies [22].

Other nootropic agents: Combination with citicoline (recognan) has been studied in chronic cerebrovascular pathology and appears to produce additive cognitive benefit [10]. Combination with memantine has been studied in cognitive impairment with preliminary evidence of additive benefit [23]. Combination with piracetam, cerebrolysin, or other nootropic agents has not been systematically studied for interactions but is used in Russian clinical practice without reported adverse interaction.

Psychoactive agents: The psychoactivating properties of Cortexin may produce additive stimulant effects with caffeine, methylphenidate, or amphetamine derivatives. The psychoactivating effect may also interfere with sedative or hypnotic agents if administered in the evening.

Local anesthetics (reconstitution diluent): Procaine (0.5 percent) or lidocaine (0.5 percent) used as the reconstitution diluent may interact with concurrent local anesthetic administration at other sites, though the small systemic dose from intramuscular injection (less than 10 mg of procaine per injection) is unlikely to produce clinically significant additive local anesthetic effects.

Cholinesterase inhibitors: Concurrent donepezil, rivastigmine, or galantamine therapy is plausible in patients with cognitive impairment and is not contraindicated. The neurotrophic mechanism of Cortexin is distinct from and potentially complementary to cholinesterase inhibition.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in clinical studies and pharmacovigilance data (over 20 years of post-marketing surveillance in the Russian Federation) are [5, 8, 25]:

- Injection site reactions (pain, redness, swelling): 8 to 15 percent of patients. Typically mild, localized to the deltoid or gluteal injection site, and resolving spontaneously within 24 to 72 hours. Pain at injection is the most common local reaction (8 to 12 percent), followed by erythema or swelling. Use of procaine or lidocaine as the reconstitution diluent substantially reduces injection site pain.
- Headache: 5 to 12 percent. Usually mild to moderate intensity, occurring during or within 2 to 4 hours of injection, and resolving spontaneously within 2 to 4 hours without specific treatment.
- Dizziness or lightheadedness: 3 to 8 percent. Typically mild, occurring within 30 minutes of intramuscular injection, with episodes usually brief (20 to 60 minutes) and self-limited.
- Nausea: 2 to 4 percent. Usually mild and very brief (15 to 45 minutes).
- Agitation, nervousness, or restlessness: 1 to 3 percent. More common at higher doses (20 mg) or with afternoon or evening administration. The psychoactivating effect is the basis for the recommendation to administer in the morning or early afternoon.
- Transient rise in body temperature: reported infrequently, generally resolving within hours.
- Asthenia: reported infrequently.

11.2 Rare and serious adverse events

Rare adverse events reported in pharmacovigilance include [5]:

- Anaphylactic shock: rare, reported in isolated cases in patients with known sensitivity to animal-derived protein preparations.

- Angioneurotic edema: rare.
- Skin rash, itching, and urticaria: infrequent, consistent with hypersensitivity to animal-derived protein components.
- Psychomotor agitation: rare, principally at higher doses or with evening administration.

No deaths attributable to Cortexin have been reported in the published clinical or pharmacovigilance literature. No organ toxicity (hepatic, renal, hematological, or cardiac) has been reported at registered doses. The systematic review of animal-derived nootropics (Perera et al. 2021) noted no safety concerns in the available Cortexin clinical data [13].

11.3 Contraindications

Cortexin is contraindicated in patients with known hypersensitivity to the active substance or to any component of the preparation (including glycine as excipient). The Russian prescribing information states that the compound has not been adequately studied in pregnancy and should be used in pregnant women only when the expected benefit exceeds the potential risk. Use during lactation follows the same risk-benefit consideration [5].

11.4 Safety in special populations

Pediatric safety: The compound has demonstrated a favorable safety profile in pediatric populations from the neonatal period through adolescence. In the cerebral palsy with epilepsy trial, aggravation of seizures occurred in only 1 of 84 patients (1.2 percent), a rate described as significantly lower than the seizure aggravation rate expected from antiepileptic drug therapy alone [11]. The multicenter pediatric cognitive dysfunction study also reported good tolerability [25].

Geriatric safety: The compound is used in elderly populations for chronic cerebral ischemia without dose adjustment. The safety profile in geriatric patients is consistent with the general adult population [8].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five neuroprotective alternatives against Cortexin, evaluated against 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 the principal neuroprotective agents that share either the tissue-derived peptide mechanism, the nootropic indication, or the clinical positioning of Cortexin within the broader neuroprotective pharmacotherapy space.

12.1 Cerebrolysin (EVER Neuro Pharma)

Mechanism: Cerebrolysin is a porcine whole-brain hydrolysate containing approximately 25 percent low-molecular-weight peptides and 75 percent free amino acids, obtained by standardized enzymatic hydrolysis of porcine brain tissue. The mechanism is pleiotropic and includes neurotrophic, neuroprotective, antioxidant, and anti-inflammatory activities analogous to Cortexin but derived from whole brain rather than cortex-specific tissue [6, 13].

Development trajectory: Cerebrolysin has the longest clinical history and largest international evidence base among tissue-derived neuropeptide preparations. It is registered in over 40 countries (though not in the United States or most Western European countries) for the treatment of stroke, traumatic brain injury, and dementia. Multiple multicenter randomized controlled trials have been conducted, including the CASTA trial (acute ischemic stroke, 1070 patients) and the CARS trial [13, 27].

Novelty: Low. The mechanism and product class are well established (first clinical use in the 1970s). Cerebrolysin is the reference compound for the tissue-derived neuropeptide class.

Effect size: A Cochrane systematic review of Cerebrolysin for acute ischaemic stroke concluded that while some studies reported improvement in neurological function and activities of daily living, the overall evidence was of very low cer-

tainty with high risk of bias [27]. Summary meta-analyses of animal-derived nootropics in cognitive disorders suggested potentially beneficial effects on cognition and global function in the short term [13].

Promising potential: Moderate. The compound remains in clinical use in many countries and in active clinical research, though the absence of approval in the United States and Western Europe limits global uptake.

Side-effect profile: Generally well tolerated. The principal adverse events are dizziness, headache, and injection site reactions with intravenous administration. A Cochrane review found no significant difference in serious adverse events between Cerebrolysin and placebo [27].

Overall validation: Moderate. The compound has the most extensive clinical evidence base among tissue-derived neuropeptide preparations, though the evidence quality has been consistently rated as low to very low by systematic reviewers applying international standards.

Comparison to Cortexin: Cerebrolysin and Cortexin are closely related preparations with similar mechanisms but important compositional and pharmacological differences. Cerebrolysin is derived from whole porcine brain and administered intravenously, while Cortexin is derived specifically from cerebral cortex and administered intramuscularly. The intravenous route of Cerebrolysin allows higher dosing (up to 30 to 50 mL daily) compared with the intramuscular route of Cortexin (10 to 20 mg). Cerebrolysin has a substantially larger international evidence base. A direct comparison in rat ischemia models found comparable neuroprotective efficacy [6]. In Russian clinical practice, the choice between Cortexin and Cerebrolysin is influenced by route of administration preference, availability, cost, and clinician experience. Cortexin has reported advantages in cost-effectiveness and absence of side effects in a comparative clinical study [26].

12.2 Actovegin (Takeda)

Mechanism: Actovegin is a deproteinized hemoderivative of calf blood, containing low-molecular-weight components including amino acids, oligopeptides, nucleosides, oligosaccharides, glycolipids, and intermediate products of fatty acid metabolism. The mechanism involves enhancement of cellular oxygen uptake and glucose utilization, with antioxidant and anti-ischemic properties [6, 13].

Development trajectory: Actovegin has been used clinically since the 1970s, primarily in German-speaking countries and in Russia, for peripheral arterial disease, diabetic polyneuropathy, and cerebrovascular disorders. The ARTEMIDA trial (Actovegin in treatment of patients with post-stroke cognitive impairment, 503 patients) was the largest international trial and demonstrated improvement in cognitive function over 6 months with sustained benefit at 12 months [28].

Novelty: Low. The compound has been in clinical use for over 50 years.

Effect size: The ARTEMIDA trial reported statistically significant cognitive improvement in post-stroke patients. Preclinical comparison in rat ischemia models found Actovegin to be inferior to both Cortexin and Cerebrolysin in neuroprotective efficacy [6].

Promising potential: Low to moderate. The compound is not approved in the United States. Its use in Europe has declined. Active clinical use continues in Russia and some Eastern European countries.

Side-effect profile: Generally well tolerated. Rare hypersensitivity reactions have been reported. The preparation is derived from calf blood, raising theoretical concerns regarding bovine spongiform encephalopathy, though manufacturing processes are designed to mitigate this risk.

Overall validation: Low to moderate. The ARTEMIDA trial provides the strongest evidence for cognitive endpoints, but the overall evidence base is small by international standards.

Comparison to Cortexin: Actovegin and Cortexin differ fundamentally in source material (calf blood versus cerebral cortex tissue) and proposed mechanism (metabolic enhancement versus neurotrophic peptide signaling). The direct preclinical comparison in ischemia models favored Cortexin [6]. Cortexin has the advantage of cortex-specific targeting and demonstrated blood-brain barrier penetration; Actovegin has the advantage of intravenous dosing flexibility and the ARTEMIDA trial as a positive international RCT.

12.3 Citicoline (various manufacturers)

Mechanism: Citicoline (cytidine-5-diphosphocholine, CDP-choline) is an endogenous nucleotide that serves as an intermediate in the synthesis of phosphatidylcholine, a major component of neuronal cell membranes. The mechanism involves

membrane stabilization, cholinergic neurotransmission enhancement, and neuroprotection through preservation of cardiolipin and sphingomyelin in mitochondrial and plasma membranes [29].

Development trajectory: Citicoline is one of the most extensively studied nootropic agents globally, with clinical trials in stroke, traumatic brain injury, cognitive impairment, and glaucoma. The ICTUS trial (International Citicoline Trial on acUte Stroke, 2298 patients) was the pivotal international stroke trial; it did not demonstrate significant benefit of citicoline over placebo on the primary endpoint [29]. Post-hoc analyses and subgroup analyses have suggested benefit in moderate-severity stroke.

Novelty: Low. The compound has been in clinical and research use for over 40 years.

Effect size: The ICTUS trial was negative on its primary endpoint. Smaller trials and meta-analyses have suggested modest cognitive benefits in vascular cognitive impairment and Alzheimer's disease [29].

Promising potential: Moderate. The compound is widely available, has an extensive safety database, and continues to be studied in cognitive applications. It is approved as a pharmaceutical in some countries and sold as a dietary supplement in others (including the United States).

Side-effect profile: Excellent tolerability. The principal adverse events are mild gastrointestinal disturbance and headache. Serious adverse events are rare.

Overall validation: Moderate. The large evidence base is offset by the negative pivotal stroke trial.

Comparison to Cortexin: Citicoline and Cortexin differ fundamentally in pharmacological class (single defined molecule versus heterogeneous peptide mixture) and in route of administration (oral or intravenous versus intramuscular). Citicoline has a substantially larger international evidence base and wider global availability. Cortexin has the potential advantage of multi-target neurotrophic activity through its peptide composition, whereas citicoline acts primarily through a single membrane-synthetic mechanism. The two agents have been studied in combination in Russian clinical practice with reported additive benefit [10].

12.4 Piracetam (various manufacturers)

Mechanism: Piracetam is a synthetic cyclic derivative of gamma-aminobutyric acid (GABA) and the prototype of the racetam class of nootropics. The mechanism involves modulation of membrane fluidity, enhancement of mitochondrial function, and improvement of neurotransmitter release without direct receptor agonism or antagonism. Proposed molecular targets include the AMPA receptor (positive allosteric modulation) and mitochondrial electron transport chain complexes [30].

Development trajectory: Piracetam was synthesized in 1964 by UCB Pharma and has been studied in over 100 clinical trials spanning cognitive impairment, stroke, vertigo, myoclonus, and dyslexia. It is approved as a pharmaceutical in many European and Asian countries but not in the United States (where it is sold as a dietary supplement).

Novelty: Very low. The compound is the oldest synthetic nootropic in clinical use.

Effect size: Clinical trials have reported modest cognitive benefits in vascular dementia and age-related cognitive decline. A Cochrane review of piracetam for dementia concluded that piracetam produced a statistically significant improvement on the Clinical Global Impression of Change but that the clinical significance of this improvement was unclear [30].

Promising potential: Low. The compound is no longer the subject of active clinical development. It continues to be used clinically in some jurisdictions and as a dietary supplement.

Side-effect profile: Excellent tolerability. The principal adverse events are insomnia, nervousness, and mild gastrointestinal disturbance. Serious adverse events are rare.

Overall validation: Moderate. The compound has the most extensive clinical research history among synthetic nootropics, though the evidence for meaningful clinical benefit remains debated.

Comparison to Cortexin: Piracetam and Cortexin represent fundamentally different pharmacological approaches to neuroprotection and cognitive enhancement. Piracetam is a single synthetic molecule with a defined (if not fully elucidated) mechanism; Cortexin is a biological preparation with pleiotropic activity from multiple peptide fractions. Piracetam has oral bioavailability and a larger

global evidence base; Cortexin requires intramuscular injection but provides multi-target neurotrophic activity. In Russian clinical practice, the two agents are sometimes used sequentially (Cortexin courses followed by oral piracetam maintenance) [15].

12.5 Semax (Institute of Molecular Genetics, Russian Academy of Sciences)

Mechanism: Semax is a synthetic heptapeptide (Met-Glu-His-Phe-Pro-Gly-Pro) based on the amino acid sequence 4 to 10 of adrenocorticotrophic hormone (ACTH), with a C-terminal Pro-Gly-Pro tripeptide extension that confers resistance to peptidase degradation. The mechanism involves activation of melanocortin receptors (MC3R and MC4R), neurotrophic factor induction (BDNF, NGF), modulation of dopaminergic and serotonergic transmission, and anti-inflammatory and antioxidant activity [31].

Development trajectory: Semax was developed at the Institute of Molecular Genetics of the Russian Academy of Sciences and received pharmaceutical registration in the Russian Federation in 1996. It is administered intranasally at 200 to 600 micrograms per day for cognitive enhancement and at 3 to 12 mg per day for acute ischemic stroke. Clinical trials in Russia have reported improvements in cognitive function, neurological recovery after stroke, and optic nerve neuropathy [31].

Novelty: Moderate. As a synthetic peptide with a defined sequence and characterized receptor pharmacology, Semax represents a more modern and molecularly defined approach than the tissue-derived peptide class.

Effect size: Clinical trials report improvements in cognitive function and neurological recovery in stroke, with effect sizes broadly comparable to those reported for Cortexin in similar indications. The evidence base is principally Russian-language and has similar quality limitations to the Cortexin literature [31].

Promising potential: Moderate. The compound is registered in Russia and has an established clinical use pattern. The defined peptide sequence and characterized receptor pharmacology are advantages for international development, but no international regulatory submission has been attempted.

Side-effect profile: Favorable. The intranasal route avoids injection site reactions. Headache and mild nasal irritation are the principal adverse events. No serious adverse events have been reported.

Overall validation: Low to moderate. The evidence base is principally Russian-language. The molecular definition (single peptide sequence, characterized receptor targets) provides a stronger mechanistic foundation than Cortexin, but the clinical evidence quality is similar.

Comparison to Cortexin: Semax and Cortexin represent two different generations of Russian neuropeptide pharmacology. Cortexin is a first-generation tissue-derived bio regulator with pleiotropic, incompletely characterized activity from a heterogeneous peptide mixture. Semax is a second-generation synthetic peptide with a defined amino acid sequence, characterized receptor pharmacology, and a non-invasive (intranasal) route of administration. Semax has the advantages of molecular definition, intranasal delivery, and a more precisely characterizable mechanism; Cortexin has the advantage of broader pleiotropic activity from multiple peptide fractions and a larger clinical evidence base in cerebrovascular indications.

12.6 Comparator summary

The five comparators occupy distinct positions in the neuroprotective pharmacotherapy space. **Cerebrolysin** is the closest structural relative to Cortexin (tissue-derived neuropeptide preparation) and has the largest international evidence base among the tissue-derived agents, though evidence quality remains low by international standards. **Actovegin** is a blood-derived preparation with a different mechanism (metabolic enhancement) that was inferior to Cortexin in direct preclinical comparison. **Citicoline** is a molecularly defined nootropic with the largest international evidence base overall but a negative pivotal stroke trial. **Piracetam** is the oldest and most widely used synthetic nootropic with modest clinical evidence. **Semax** is a synthetic peptide with defined pharmacology representing a more modern approach to neuropeptide therapeutics.

Cortexin occupies a unique position as the only cortex-specifically sourced neuropeptide preparation among the comparators, the only intramuscularly administered tissue-derived neuropeptide, and the agent with the most extensive Russian-language clinical evidence base in pediatric neurological indications. Its principal limitation relative to the comparators is the absence of international regulatory-grade evidence. The practical positioning of Cortexin in the neuroprotective re-

search landscape is as a multi-target biological agent with established clinical use in the Russian Federation, substantial but methodologically limited clinical evidence, and a pharmacological profile that complements rather than duplicates the mechanisms of the synthetic nootropic comparators.

Investigators considering Cortexin for neuroprotective research should understand that the compound is not directly comparable to single-molecule therapeutics in terms of pharmacological precision, batch reproducibility, or regulatory classification. Its strengths are the pleiotropic activity from multiple bioactive peptide fractions, the cortex-specific sourcing, the established clinical use in a large patient population, and the favorable safety profile. Its limitations are the inherent batch variability of a biological preparation, the absence of international regulatory-grade clinical evidence, the requirement for intramuscular injection, and the difficulty of conducting conventional pharmacokinetic and pharmacodynamic characterization on a heterogeneous mixture.

13. References

1. Khavinson VK, Kuznik BI, Ryzhak GA. Peptide bioregulators: a new class of geroprotectors. Message 1: results of experimental studies. Adv Gerontol. 2013;26(1):20-37.
2. Khavinson VK. Peptides and ageing. Neuroendocrinol Lett. 2002;23(Suppl 3):11-144.
3. Skvortsova VI, Stakhovskaya LV, Gubskiy LV, et al. A randomized, double-blind, placebo-controlled study of Cortexin efficacy and safety in acute hemispheric ischemic stroke. Zhurnal Nevrologii i Psikhatrii. 2012;112(1):48-54.
4. GEROPHARM LLC. Cortexin product monograph: amino acid composition analysis. Saint Petersburg, Russia. Internal technical documentation.
5. GEROPHARM LLC. Cortexin prescribing information (summary of product characteristics). Russian Federation pharmaceutical register. Registration certificate P N000514/01.
6. Gulyaev MV, Pryanikova NA, Timashev PS, et al. Neuroprotective action of Cortexin, Cerebrolysin and Actovegin in acute or chronic brain ischemia in rats. PLoS One. 2021;16(7):e0254493.
7. Granstrem OK, Sorokina EG, Stelmashook EV, et al. Molecular mechanisms of brain peptide-containing drugs: cortexin. Neurosci Behav Physiol. 2019;49(7):844-848.
8. Fedin AI, Zakharov VV, Tanashyan MM, et al. Dose-dependent effects of cortexin in chronic cerebral ischemia (results of a multicenter randomized controlled study). Zhurnal Nevrologii i Psikhatrii. 2018;118(9):35-42.
9. Skoromets AA, Stambovskaya AA, Shamrey DV, et al. An open clinical trial of cortexin in treatment of brain ischemia. Zhurnal Nevrologii i Psikhatrii. 2008;108(Suppl):20-26.
10. Chukanova EI, Chukanova AS. A multicenter observation study of the efficacy of cortexin and recognan (citicoline) in the treatment of cognitive impairment in chronic cerebrovascular pathology. Zhurnal Nevrologii i Psikhatrii. 2019;119(2):34-40.

11. Badalyan OL, Burd SG, Savenkov AA, et al. Peptidergic nootropic therapy in cerebral palsy associated with epilepsy. Zhurnal Nevrologii i Psikhatrii. 2017;117(10):55-61.
12. Evsyukova II, Maslyanyuk NA, Saveleva GM. Efficacy of cortexin in treatment of perinatal CNS lesions in premature neonates. Zhurnal Nevrologii i Psikhatrii. 2008;108(12):83-86.
13. Perera T, Tan JL, Cole MH, et al. The efficacy and safety of animal-derived nootropics in cognitive disorders: systematic review and meta-analysis. Aging Brain. 2021;1:100009.
14. Khavinson VK, Linkova NS, Polyakova VO, et al. Peptide bioregulation of aging: results and prospects. Biogerontology. 2009;10(6):649-661.
15. Belova AN, Shakurova DN, Balaev IM. Cortexin in the rehabilitation of patients with neurological disorders. Zhurnal Nevrologii i Psikhatrii. 2014;114(4):46-51.
16. Verclytte S, Bhide R, Shah A, et al. Prospective, double blinded, comparative assessment of the pharmacological activity of Cerebrolysin and distinct peptide preparations for the treatment of embolic stroke. J Neurol Sci. 2019;399:131-137.
17. Poletaeva OG, Tereshkina EB, Stelmashook EV, et al. Cortexin: molecular mechanisms and targets of neuroprotective activity. Zhurnal Nevrologii i Psikhatrii. 2015;115(11):99-104.
18. Koroleva SV, Saranstseva SV. Neuroprotective effects of peptide bioregulators in people of different ages. Adv Gerontol. 2014;27(4):671-676.
19. Kozina LS, Arutjunyan AV, Stvolinskiy SL, et al. Cortexin restores the ratio of pro- and antioxidative systems in accelerated aging model in rats. Adv Gerontol. 2012;25(3):431-436.
20. Zueva MV, Neroev VV, Tsapenko IV, et al. Neurotropic effects of cortexin on models of mental and physical developmental delay. Biomedicines. 2025;13(4):860.
21. Koroleva SV, Kutyreva AV, et al. Comparative study of protective effects of Cortexin, Cerebrolysin and Actovegin on memory impairment, cerebral circulation and morphological changes in the hippocampus of rats with chronic brain ischemia. Zhurnal Nevrologii i Psikhatrii. 2020;120(8):28-35.

22. Baturin VA, Chernov YN, Baturina MV. Evaluation of the efficacy and safety of application of the drug cortexin in the complex rehabilitation of verticalization in patients with ischemic stroke in the acute period. *Zhurnal Nevrologii i Psikhatrii*. 2019;119(9):65-70.
 23. Yakhno NN, Zakharov VV, Lokshina AB. The efficacy of cortexin and memantinol (memantine) in the treatment of cognitive impairment in patients with chronic cerebral ischemia. *Zhurnal Nevrologii i Psikhatrii*. 2018;118(1):33-38.
 24. Shabanov PD, Lebedev AA, Stetsenko VP, et al. Comparison of behavioral effects of cortexin and cerebrolysin injected into brain ventricles. *Bull Exp Biol Med*. 2007;144(4):531-534.
 25. Zavadenko NN, Kozlova EV, Zaytseva OV. Results of a multicenter study on the efficacy of cortexin in treatment of cognitive dysfunction in children. *J Neurol Stroke*. 2017;7(4):00253.
 26. Rummyantseva SA, Afanasyev VV, Silina EV, et al. Comparative analysis of efficacy of certain neuroprotectors in ischemic stroke. *Zhurnal Nevrologii i Psikhatrii*. 2008;108(1):26-31.
 27. Ziganshina LE, Abakumova T, Vernay L. Cerebrolysin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2023;10:CD007026.
 28. Guekht A, Skoog I, Edmundson S, Zakharov V, Korczyn AD. ARTEMIDA trial (a randomized trial of efficacy, 12 months international double-blind Actovegin): a randomized controlled trial to assess the efficacy of Actovegin in poststroke cognitive impairment. *Stroke*. 2017;48(5):1262-1270.
 29. Davalos A, Alvarez-Sabin J, Castillo J, et al. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet*. 2012;380(9839):349-357.
 30. Flicker L, Grimley Evans J. Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev*. 2001;2:CD001011.
 31. Ashmarin IP, Nezavibatko VN, Levitskaya NG, et al. Design and investigation of an ACTH(4-10) analogue lacking D-amino acids and hydrophobic radicals. *Neurosci Res Commun*. 1995;16(2):105-112.
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