

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cytoflavin

A four-component metabolic combination drug developed by POLYSAN Ltd. that supplies Krebs cycle substrate, purine nucleoside, NAD⁺ precursor, and FAD cofactor to restore aerobic energy production in ischemic, hypoxic, and neurodegenerative tissue.

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ABSTRACT

Cytoflavin is a fixed-dose combination metabolic agent comprising succinic acid (the principal mass component and Krebs cycle substrate), inosine (a purine nucleoside and precursor to adenine nucleotides), nicotinamide (the amide form of vitamin B3 and precursor to nicotinamide adenine dinucleotide), and riboflavin (vitamin B2, the precursor to flavin adenine dinucleotide and flavin mononucleotide). Developed and manufactured by POLYSAN Scientific and Technological Pharmaceutical Company (Saint Petersburg, Russia), the product is formulated as enteric-coated tablets (300 mg succinic acid, 50 mg inosine, 25 mg nicotinamide, 5 mg riboflavin per tablet) and as a concentrate for intravenous infusion (1000 mg succinic acid, 200 mg inosine, 100 mg nicotinamide, 20 mg riboflavin sodium phosphate per 10 mL ampoule, with meglumine and sodium hydroxide as excipients). The pharmacological rationale is the simultaneous provision of four complementary metabolic substrates and cofactors whose intracellular availability becomes rate-limiting during ischemia, hypoxia, and oxidative stress: succinic acid feeds directly into mitochondrial Complex II (succinate dehydrogenase), bypassing the NAD-dependent steps of the Krebs cycle that fail under hypoxic conditions; inosine supports purine salvage and ATP resynthesis; nicotinamide replenishes the NAD⁺ pool consumed by poly(ADP-ribose) polymerase activation during ischemic injury; and riboflavin provides the FAD prosthetic group required for succinate dehydrogenase function and for multiple flavoprotein-dependent antioxidant enzymes including glutathione reductase.

The clinical evidence base for Cytoflavin spans ischemic stroke (acute and chronic cerebral ischemia), traumatic brain injury, diabetic polyneuropathy, postoperative cognitive decline in elderly surgical patients, post-COVID-19 asthenic syndrome, and organic asthenic disorder. The largest and most rigorous published trial is the CYLINDER study, a multicenter, double-blind, placebo-controlled, randomized trial in 216 patients with type 2 diabetes mellitus and symptomatic distal sensorimotor diabetic polyneuropathy conducted across 10 Russian clinical centers, which reported a statistically significant reduction in Total Symptom Score (TSS change of negative 2.65 points in the experimental group versus negative 1.73 points in the placebo group, p less than 0.001) after a sequential intravenous-then-oral treatment regimen. In acute ischemic stroke, multicenter studies have demonstrated marked reduction in neurological deficit severity by day 10 and higher probability of favorable functional outcome compared to standard-of-care controls. The CITADEL prospective randomized study demonstrated a pronounced anti-asthenic effect and correction of cognitive impairments in post-COVID-19 rehabilitation. An international, multicenter, randomized, single-blind, placebo-controlled trial (NCT04631484) evaluating Cytoflavin in moderate traumatic brain injury in adults was completed in 2024, with results published in *Frontiers in Neurology* in 2025, representing the first large-scale international trial of the compound outside the Russian Federation and Commonwealth of Independent States.

Cytoflavin is registered as a medicinal product in the Russian Federation and in Vietnam. The manufacturing facility holds GMP EU certification. The compound is not approved by the United States Food and Drug Administration, by the European Medicines Agency, or by other major Western regulatory authorities. The

clinical literature is predominantly in Russian-language journals, with an expanding body of English-language publications in international peer-reviewed venues. The safety profile across published clinical studies is favorable; the principal adverse events are transient epigastric discomfort, headache, hyperuricemia (attributable to inosine-derived purine catabolism), and rare hypersensitivity reactions. No serious adverse events attributable to the drug have been reported in published controlled trials.

This monograph reviews the composition, identification, and formulation chemistry of Cytoflavin; the individual and composite pharmacology of its four active components; the pharmacokinetic considerations for each component; the preclinical pharmacology; the clinical evidence base across all studied indications; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety signals; and a comparative assessment of five alternative neuroprotective metabolic agents (Mexidol, Actovegin, Cerebrolysin, citicoline, and Reamberin) against Cytoflavin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Product name: Cytoflavin (transliterated from Russian: Tsitoflavin).

Marketed names: Cytoflavin (POLYSAN Ltd., Russian Federation); Citoflavin (alternative transliteration used in some international registrations and clinical trial records).

Manufacturer: Scientific and Technological Pharmaceutical Firm POLYSAN Ltd. (STPF POLYSAN), Saint Petersburg, Russian Federation.

Registration status: Registered medicinal product in the Russian Federation (Ministry of Health registration). Registered in Vietnam. Not registered by the United States Food and Drug Administration, the European Medicines Agency, the Therapeutic Goods Administration (Australia), Health Canada, or the Medicines and Healthcare products Regulatory Agency (United Kingdom).

Chemical Abstracts Service registry numbers for individual active pharmaceutical ingredients:

- Succinic acid: CAS 110-15-6
- Inosine: CAS 58-63-9
- Nicotinamide: CAS 98-92-0
- Riboflavin (vitamin B2): CAS 83-88-5
- Riboflavin 5'-sodium phosphate (injectable form): CAS 130-40-5

Cytoflavin is a fixed-dose combination product and does not carry a single CAS registry number. The product is identified in clinical trial registries by its component listing: inosine plus nicotinamide plus riboflavin plus succinic acid, abbreviated INRSA in some international publications [1, 2].

ClinicalTrials.gov identifiers for registered trials: NCT04631484 (traumatic brain injury), NCT05297851 (acute stroke with reperfusion therapy), NCT05935787 (ischemic stroke without reperfusion therapy), NCT04649203 (diabetic polyneuropathy, CYLINDER study), NCT03849664 (postoperative cognitive decline in elderly patients).

1.2 Structural class and chemistry

Cytoflavin is classified as a metabolic cytoprotectant and antihypoxant. It is not a single molecular entity but a rationally designed four-component combination of endogenous metabolites and vitamin cofactors that participate in mitochondrial oxidative phosphorylation and the tricarboxylic acid (Krebs) cycle.

Succinic acid (butanedioic acid; molecular formula $C_4H_6O_4$; molecular weight 118.09 g/mol) is a dicarboxylic acid and endogenous intermediate of the Krebs cycle. It is the substrate for succinate dehydrogenase (mitochondrial Complex II), the only enzyme that participates in both the Krebs cycle and the mitochondrial electron transport chain.

Inosine (hypoxanthine riboside; molecular formula $C_{10}H_{12}N_4O_5$; molecular weight 268.23 g/mol) is a purine nucleoside formed by the deamination of adenosine. It participates in the purine salvage pathway and serves as a precursor to inosine monophosphate, adenosine monophosphate, and guanosine monophosphate, supporting ATP and GTP resynthesis under conditions of energy depletion.

Nicotinamide (niacinamide, vitamin B3 amide; molecular formula $C_6H_6N_2O$; molecular weight 122.12 g/mol) is the amide form of nicotinic acid and the direct precursor to nicotinamide adenine dinucleotide (NAD^+) through the salvage pathway enzyme nicotinamide phosphoribosyltransferase (NAMPT). NAD^+ is the principal electron carrier for the Krebs cycle dehydrogenases and for mitochondrial Complex I (NADH:ubiquinone oxidoreductase).

Riboflavin (vitamin B2; molecular formula $C_{17}H_{20}N_4O_6$; molecular weight 376.36 g/mol) is the precursor to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), which serve as prosthetic groups for succinate dehydrogenase (Complex II), electron-transferring flavoprotein dehydrogenase, and multiple flavoprotein-dependent antioxidant enzymes including glutathione reductase and thioredoxin reductase.

1.3 Formulation composition

Tablet formulation (enteric-coated): Each tablet contains succinic acid 300 mg, inosine 50 mg, nicotinamide 25 mg, and riboflavin 5 mg. Excipients include povidone, calcium stearate, and an enteric coating (Eudragit or equivalent methacrylic acid copolymer). The mass ratio of active components is approximately 79:13:7:1 (succinic acid : inosine : nicotinamide : riboflavin).

Injectable formulation (concentrate for intravenous infusion): Each 10 mL ampoule contains succinic acid 1000 mg, inosine 200 mg, nicotinamide 100 mg, and riboflavin sodium phosphate 20 mg. Excipients are meglumine (N-methylglucamine) 1650 mg, sodium hydroxide 340 mg, and water for injection to 10 mL. The meglumine and sodium hydroxide serve as buffering and solubilizing agents to maintain the solution pH and to ensure riboflavin sodium phosphate solubility. The solution is clear and yellow owing to the riboflavin content.

1.4 Patent and intellectual property

The injectable formulation of Cytoflavin is covered by Ukrainian patent UA58565C2 describing a cytoprotective injectable drug composition. The original development and formulation work was conducted at POLYSAN Ltd. in the 1990s and early 2000s. The compound entered the Russian pharmaceutical market as a registered medicinal product in the early 2000s. Multiple formulation and method-of-use patents and patent applications have been filed in the Russian Federation and in selected Commonwealth of Independent States jurisdictions [3].

2. Abstract

Cytoflavin is a fixed-dose combination metabolic cytoprotectant and antihypoxant developed by POLYSAN Ltd. (Saint Petersburg, Russia) for the treatment of conditions characterized by cerebral and peripheral tissue ischemia, hypoxia, and mitochondrial energy failure. The drug comprises four endogenous metabolites and vitamin cofactors (succinic acid, inosine, nicotinamide, and riboflavin) that collectively restore aerobic energy production by supplying substrate to mitochondrial Complex II, replenishing the NAD⁺ and FAD cofactor pools depleted during ischemic injury, and providing purine nucleoside for ATP resynthesis through the salvage pathway [4, 5].

The pharmacological rationale rests on the observation that ischemic and hypoxic injury produces a characteristic pattern of mitochondrial metabolic failure: depletion of NAD⁺ (consumed by both interrupted electron transport and by poly(ADP-ribose) polymerase activation in response to DNA damage), accumulation of NADH that inhibits the NAD-dependent Krebs cycle dehydrogenases, depletion of the adenine nucleotide pool through degradation of ATP to ADP, AMP, adenosine, inosine, and hypoxanthine, and impaired function of FAD-dependent enzymes. Cytoflavin addresses each of these bottlenecks simultaneously: succinic acid enters the Krebs cycle at Complex II (succinate dehydrogenase), which uses FAD rather than NAD⁺ as its electron acceptor and therefore remains functional when the NAD⁺/NADH ratio is collapsed; nicotinamide replenishes NAD⁺ through the salvage pathway; riboflavin provides FAD for Complex II and for antioxidant flavoproteins; and inosine supports purine salvage for nucleotide resynthesis [5, 6, 7].

The clinical development program has produced evidence across multiple neurological and metabolic indications. In acute ischemic stroke, multicenter studies have demonstrated reduction in neurological deficit by day 10 and improved functional outcomes at 90 days [8, 9]. The CYLINDER multicenter randomized double-blind placebo-controlled trial in 216 patients with diabetic polyneuropathy showed statistically significant improvement in Total Symptom Score compared to placebo [10]. The CITADEL prospective randomized study demonstrated anti-asthenic and procognitive effects in post-COVID-19 rehabilitation [11]. An international multicenter randomized placebo-controlled trial in moderate traumatic brain injury (NCT04631484) was completed in 2024 and published in 2025, extending the evi-

dence base beyond Russian and CIS populations [1]. Additional clinical evidence exists for chronic cerebral ischemia, postoperative cognitive decline in elderly patients, and organic asthenic disorder [12, 13, 14].

The drug is well tolerated. The principal adverse events across published controlled trials are mild and transient: epigastric discomfort, headache, hyperuricemia (from inosine-derived purine catabolism), transient hypoglycemia, and rare allergic reactions. No serious adverse events attributed to Cytoflavin have been reported in published controlled trials. The drug is registered in the Russian Federation and Vietnam; manufacturing complies with GMP EU standards.

3. Discovery and Development History

3.1 Origin and rationale

The development of Cytoflavin emerged from the Soviet and post-Soviet tradition of metabolic pharmacology, which emphasized the therapeutic use of endogenous metabolites and cofactors to support cellular bioenergetics under pathological conditions. POLYSAN Ltd. was established in 1992 in Saint Petersburg by a group of scientists with backgrounds in biochemistry and pharmaceutical technology. The company's research program focused on the development of injectable and oral formulations of Krebs cycle intermediates and associated cofactors for cytoprotective applications in neurology, cardiology, and critical care [15].

The conceptual basis for the Cytoflavin formulation was the recognition that ischemic and hypoxic tissue injury produces simultaneous depletion of multiple metabolic substrates and cofactors, and that single-agent supplementation (for example, succinic acid alone) addresses only one of several rate-limiting bottlenecks in mitochondrial energy production. The four-component design was intended to provide comprehensive metabolic rescue: Krebs cycle substrate (succinic acid), purine nucleoside for ATP resynthesis (inosine), NAD⁺ precursor (nicotinamide), and FAD precursor (riboflavin) [5, 6].

3.2 Preclinical development

Preclinical studies in the late 1990s and early 2000s characterized the cytoprotective properties of the combination in animal models of cerebral ischemia, global hypoxia, and toxic encephalopathy. The combination demonstrated reduction in infarct volume, improvement in neurological deficit scores, and preservation of mitochondrial membrane potential in rat models of middle cerebral artery occlusion. The preclinical pharmacology supported the clinical hypothesis that simultaneous provision of the four metabolic components produced a synergistic cytoprotective effect exceeding that of any individual component administered alone [3, 16].

3.3 Clinical development in Russia

The injectable formulation of Cytoflavin was the first to enter clinical development, with initial clinical trials in patients with acute ischemic stroke conducted in the early 2000s at neurological centers in Saint Petersburg and Moscow. These early open-label and comparator-controlled studies demonstrated reduction in neurological deficit severity, improvement in consciousness level, and favorable safety profiles at the recommended intravenous dosing regimen of 20 mL (two ampoules) diluted in 200 mL of carrier solution administered twice daily for 10 days [8, 9].

The tablet formulation was developed subsequently to enable extended oral treatment following the acute intravenous phase and to support indications requiring chronic oral dosing (chronic cerebral ischemia, asthenic disorders, diabetic neuropathy). Registration of the tablet formulation in the Russian Federation followed completion of multicentre studies in chronic cerebral ischemia [12].

3.4 International expansion

POLYSAN pursued international registration and clinical development beginning in the 2010s. The first international registration was achieved in Vietnam. The company initiated international multicenter clinical trials designed to meet more rigorous evidentiary standards including double-blind placebo-controlled randomized designs with intention-to-treat analysis. The CYLINDER study (NCT04649203) in diabetic polyneuropathy and the international traumatic brain injury trial (NCT04631484, the MITRA study) represent the transition from predominantly open-label Russian-language evidence to international, placebo-controlled, English-language publications in peer-reviewed journals [1, 10].

3.5 GMP certification and manufacturing

POLYSAN obtained GMP EU certification for its manufacturing facility, confirming compliance with European standards for medicinal product manufacturing and quality control. The company also manufactures Reamberin (meglumine sodium succinate, another succinate-based cytoprotective agent), Cycloferon (a meglumine acridone acetate immunomodulator), and Remaxol (a hepatoprotective combination) [15].

4. Mechanism of Action

The mechanism of action of Cytoflavin is the composite pharmacology of its four active components acting on interconnected targets within mitochondrial oxidative metabolism, the Krebs cycle, purine nucleotide homeostasis, and the cellular antioxidant defense system. The components are not independent drugs combined for unrelated indications; they are metabolically linked substrates and cofactors whose simultaneous provision addresses the characteristic pattern of bioenergetic failure in ischemic, hypoxic, and oxidatively stressed tissue [5, 6, 7].

4.1 Succinic acid and Complex II

Succinic acid (succinate) is the substrate for succinate dehydrogenase (SDH), the enzyme complex that catalyzes the oxidation of succinate to fumarate in the Krebs cycle and simultaneously transfers electrons to ubiquinone in the mitochondrial electron transport chain (Complex II). SDH is unique among the Krebs cycle enzymes in that it is the only one embedded in the inner mitochondrial membrane and the only one that uses FAD rather than NAD⁺ as its electron acceptor [17].

During ischemia and hypoxia, the NAD⁺/NADH ratio collapses as electron transport chain activity decreases and NADH accumulates. The NAD-dependent Krebs cycle dehydrogenases (isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, malate dehydrogenase) are progressively inhibited by NADH accumulation and NAD⁺ depletion. Complex II, because it uses FAD rather than NAD⁺, retains the capacity to accept electrons from succinate and transfer them to ubiquinone even when the NAD-dependent pathway is inhibited. Exogenous succinic acid therefore provides a bypass route for electron entry into the transport chain under hypoxic conditions, supporting residual ATP production via oxidative phosphorylation [17, 18].

The antihypoxant activity of succinic acid is the principal acute pharmacological effect of Cytoflavin. The compound also has antioxidant properties through reduction of reactive oxygen species generation at Complex I (by maintaining electron flow through Complex II and reducing the reverse electron transport that generates

superoxide at Complex I under ischemia-reperfusion conditions) and through support of the FAD-dependent glutathione reductase that regenerates reduced glutathione [7, 18].

4.2 Inosine and purine salvage

Inosine is a purine nucleoside produced endogenously by the deamination of adenosine. Under ischemic conditions, ATP is sequentially degraded to ADP, AMP, adenosine, inosine, hypoxanthine, xanthine, and uric acid. The degradation of the adenine nucleotide pool is largely irreversible through the de novo purine synthesis pathway, which is energy-intensive and slow. The purine salvage pathway, which reconverts hypoxanthine and inosine to inosine monophosphate (IMP) through the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), provides a more rapid and energy-efficient route for nucleotide resynthesis [19].

Exogenous inosine administration provides substrate for the purine salvage pathway, supporting the resynthesis of IMP, AMP, ATP, GMP, and GTP during and after ischemic insult. The functional consequence is accelerated recovery of the cellular energy charge (the ratio $[ATP + 0.5 ADP] / [ATP + ADP + AMP]$) and support of ATP-dependent cellular processes including ion pump function, protein synthesis, and signal transduction [19, 20].

Inosine has additional pharmacological activities independent of purine salvage. It activates adenosine A1 and A2A receptors at micromolar concentrations, producing anti-inflammatory and neuroprotective effects. It stimulates axonal outgrowth in cortical neurons through activation of the Mst3b kinase signaling pathway, an activity that has been characterized in models of spinal cord injury and stroke and that provides a neurotrophic component to the metabolic rescue [20].

4.3 Nicotinamide and NAD⁺ replenishment

Nicotinamide is the amide form of nicotinic acid (vitamin B3) and the direct precursor to NAD⁺ through the salvage pathway enzyme nicotinamide phosphoribosyltransferase (NAMPT, also known as visfatin). NAD⁺ is the principal electron carrier for the Krebs cycle dehydrogenases and for Complex I of the electron transport chain, and is also a substrate for poly(ADP-ribose) polymerase (PARP), sirtuins, and cyclic ADP-ribose synthases [21].

During ischemic injury, NAD⁺ is consumed by two principal mechanisms: oxidative interruption of the electron transport chain (preventing NADH reoxidation to NAD⁺) and PARP hyperactivation in response to DNA damage (which cleaves NAD⁺ to produce poly(ADP-ribose) and nicotinamide). PARP hyperactivation alone can deplete the cellular NAD⁺ pool within minutes of severe ischemic insult, producing a bioenergetic catastrophe that is a proximal cause of cell death in stroke and traumatic brain injury [21, 22].

Exogenous nicotinamide replenishes the NAD⁺ pool through the salvage pathway and simultaneously inhibits PARP activity (nicotinamide is a product inhibitor of PARP). The dual effect (NAD⁺ replenishment plus PARP inhibition) is neuroprotective in multiple animal models of cerebral ischemia and traumatic brain injury. Nicotinamide also supports sirtuin-dependent mitochondrial biogenesis and quality control pathways and has direct anti-inflammatory activity through inhibition of NF-kappaB signaling [21, 22, 23].

4.4 Riboflavin and FAD provision

Riboflavin (vitamin B2) is converted intracellularly to FMN by riboflavin kinase and subsequently to FAD by FAD synthetase. FAD is the covalently bound prosthetic group of succinate dehydrogenase (Complex II) and the prosthetic group of multiple other flavoproteins including electron-transferring flavoprotein dehydrogenase (which feeds electrons from fatty acid beta-oxidation into the electron transport chain), dihydrolipoamide dehydrogenase (the E3 component shared by the pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched-chain alpha-keto acid dehydrogenase complexes), glutathione reductase, thioredoxin reductase, and monoamine oxidases [24].

The inclusion of riboflavin in the Cytoflavin formulation ensures that the FAD prosthetic group required for Complex II function is available when exogenous succinic acid is administered, closing a potential rate-limiting step in the succinic acid antihypoxant mechanism. The antioxidant contribution (through glutathione reductase and thioredoxin reductase support) provides an additional layer of cytoprotection [24].

4.5 Composite mechanism and synergy

The four components of Cytoflavin address complementary nodes in the mitochondrial energy failure cascade. The composite mechanism can be summarized as follows: riboflavin provides FAD for Complex II; succinic acid provides substrate for FAD-dependent Complex II, bypassing the NAD-dependent Krebs cycle bottleneck; nicotinamide replenishes NAD⁺ and inhibits PARP-mediated NAD⁺ consumption; and inosine supports ATP resynthesis through purine salvage. The rationale predicts that the combination will produce a greater cytoprotective effect than any single component, a prediction supported by preclinical comparisons in which the four-component combination produced greater infarct volume reduction and neurological improvement than equimolar doses of individual components in rat models of cerebral ischemia [5, 6, 16].

The antioxidant component of the mechanism is similarly composite: succinic acid reduces reverse electron transport at Complex I (reducing superoxide generation), riboflavin supports glutathione reductase (regenerating reduced glutathione for glutathione peroxidase-mediated peroxide detoxification), and nicotinamide supports NADPH generation through the NAD kinase pathway (NADPH being the electron donor for both glutathione reductase and thioredoxin reductase) [7].

5. Pharmacokinetics

The pharmacokinetics of Cytoflavin reflect the individual disposition of its four active components, all of which are endogenous metabolites with established metabolic pathways. No compartmental pharmacokinetic modeling of the combination product has been published in the international literature; the available pharmacokinetic data derive from the individual component literature and from the product prescribing information [4, 5].

5.1 Succinic acid

Succinic acid is rapidly absorbed from the gastrointestinal tract after oral administration of enteric-coated tablets. Following absorption, succinic acid enters the mitochondrial matrix through the dicarboxylate carrier and is oxidized by succinate dehydrogenase to fumarate; the half-life of exogenous succinate in plasma is extremely short (minutes) owing to rapid cellular uptake and metabolic utilization. The product is fumarate, which continues through the Krebs cycle to produce malate, oxaloacetate, and citrate. Complete oxidation yields carbon dioxide and water. There are no pharmacologically active metabolites requiring renal or hepatic elimination; succinic acid is completely metabolized through endogenous pathways [18].

After intravenous administration, succinic acid distributes rapidly to tissues with high mitochondrial density (brain, heart, kidney, liver, skeletal muscle). Peak tissue concentrations are achieved within minutes of infusion completion. The rapid metabolic clearance means that the pharmacological effect is largely concurrent with the infusion period and the immediate post-infusion interval.

5.2 Inosine

Inosine is absorbed from the gastrointestinal tract with moderate bioavailability. Following absorption, inosine is metabolized by purine nucleoside phosphorylase to hypoxanthine and ribose-1-phosphate. Hypoxanthine enters the purine salvage pathway (conversion to IMP by HGPRT) or is oxidized by xanthine oxidase to xan-

thine and then to uric acid. The terminal metabolite uric acid is excreted by the kidneys. Plasma half-life of exogenous inosine is approximately 1 to 3 hours in healthy subjects [19, 20].

The inosine component is the source of the hyperuricemia adverse event signal: exogenous inosine administration increases the uric acid load through xanthine oxidase-mediated catabolism, and patients with pre-existing hyperuricemia or gout are at increased risk of exacerbation.

5.3 Nicotinamide

Nicotinamide is well absorbed from the gastrointestinal tract with high oral bioavailability (approaching 100 percent). It is converted to NAD⁺ through the salvage pathway (NAMPT converts nicotinamide to nicotinamide mononucleotide; nicotinamide mononucleotide adenylyltransferase converts NMN to NAD⁺). The plasma half-life of nicotinamide at pharmacological doses is approximately 3 to 5 hours. Hepatic metabolism produces N-methylnicotinamide and 2-pyridone and 4-pyridone derivatives, which are excreted in urine. Nicotinamide does not produce the vasodilatory flushing characteristic of nicotinic acid (niacin) because it does not activate the GPR109A receptor [21, 22].

5.4 Riboflavin

Riboflavin absorption from the gastrointestinal tract is saturable and carrier-mediated, with maximal absorption at single oral doses of approximately 25 to 30 mg. Absorption occurs primarily in the proximal small intestine via the riboflavin transporter (RFVT2/SLC52A2). Following absorption, riboflavin is converted to FMN by riboflavin kinase and to FAD by FAD synthetase, principally in the liver, kidney, and brain. Plasma protein binding is moderate (approximately 60 percent, primarily to albumin and immunoglobulins). Excess riboflavin and its metabolites are excreted in urine (producing the characteristic yellow discoloration). The plasma half-life is approximately 1 to 2 hours, though tissue retention of FAD and FMN is longer [24].

In the injectable formulation, riboflavin is supplied as riboflavin 5'-sodium phosphate (riboflavin phosphate, the soluble form of FMN), which has immediate bioavailability and does not require the initial phosphorylation step. The yellow color of the injectable solution is attributable to the riboflavin content.

5.5 Routes of administration

Intravenous infusion: The primary acute-care route. The contents of one or two ampoules (10 to 20 mL) are diluted in 100 to 200 mL of 0.9 percent sodium chloride solution or 5 to 10 percent dextrose solution and administered by intravenous infusion at a rate not exceeding 4.3 mL per minute (approximately 90 drops per minute). The standard acute treatment course is 10 days of twice-daily infusions. The rate limitation reflects the need to avoid transient vasodilation and tachycardia from rapid succinate delivery.

Oral tablets: Two enteric-coated tablets taken twice daily (total daily dose: succinic acid 1200 mg, inosine 200 mg, nicotinamide 100 mg, riboflavin 20 mg), at least 30 minutes before meals, with 100 mL of water, without chewing. The interval between doses should be 8 to 10 hours. The standard oral treatment course is 25 days. The evening dose should be administered no later than 18:00 hours to avoid potential sleep disturbance from the metabolic activation effect. Enteric coating prevents gastric irritation from succinic acid.

5.6 Special populations

No formal pharmacokinetic studies in special populations (renal impairment, hepatic impairment, pediatric, geriatric) have been published in the international literature for the combination product. The individual components are endogenous metabolites with established safety profiles across populations. The prescribing information recommends caution in patients with nephrolithiasis (uric acid stones, owing to the inosine-derived hyperuricemia), in patients with gout, and in patients with known hypersensitivity to any of the components. Pregnancy and lactation data are limited; the prescribing information recommends use only when clearly indicated [4].

6. Preclinical Pharmacology

6.1 Cerebral ischemia models

Preclinical studies of Cytoflavin in rat models of focal cerebral ischemia (middle cerebral artery occlusion) demonstrated dose-dependent reduction in infarct volume, improvement in neurological deficit scores, and preservation of mitochondrial membrane potential in ischemic penumbra tissue when the combination was administered intravenously during the first hours of reperfusion. The four-component combination produced greater cytoprotective effect than equimolar doses of succinic acid alone, inosine alone, nicotinamide alone, or riboflavin alone, supporting the synergy hypothesis of the formulation design [3, 16].

6.2 Global hypoxia models

In acute normobaric and hypobaric hypoxia models in mice and rats, Cytoflavin administration increased survival time and reduced post-hypoxic neurological deficit. The antihypoxant effect correlated with preservation of cerebral ATP content and with maintenance of the NAD⁺/NADH ratio in brain tissue homogenates [5, 6].

6.3 Toxic encephalopathy models

In models of alloxan-induced diabetes in mice, Cytoflavin and its individual components were evaluated for effects on behavioral disorders. The combination produced improvement in anxiety-like behavior and cognitive function in diabetic mice, with the effect of the combination exceeding that of individual components [25].

6.4 Mitochondrial function studies

In vitro studies of isolated mitochondria from rat brain demonstrated that the combination of succinic acid and riboflavin maintained Complex II (succinate dehydrogenase) activity under conditions of FAD depletion, confirming the mechanistic ra-

tionale for their co-administration. Nicotinamide addition restored NAD-dependent dehydrogenase activity and reduced PARP-mediated NAD⁺ consumption in a dose-dependent manner [5, 7].

6.5 Anti-inflammatory and antioxidant effects

Preclinical studies demonstrated that Cytoflavin administration reduced serum and tissue markers of oxidative stress (malondialdehyde, protein carbonyls) and inflammatory cytokines (tumor necrosis factor alpha, interleukin-6) in ischemia-reperfusion models. The antioxidant effect was attributed to the composite mechanism described in section 4.5 [7, 16].

7. Clinical Evidence Base

7.1 Acute ischemic stroke

The earliest clinical applications of Cytoflavin were in the treatment of acute ischemic stroke. A multicenter study enrolled 70 patients (41 in the treatment group and 29 in the control group) with acute cerebral infarction, with treatment initiated within the first 24 hours of symptom onset. Cytoflavin was administered intravenously at 20 mL (two ampoules) diluted in 200 mL of 0.9 percent sodium chloride, twice daily for 10 days. The treatment group demonstrated marked reduction in the severity of neurological symptoms by day 10 (assessed by the National Institutes of Health Stroke Scale) and a higher probability of favorable functional outcome compared to the control group receiving standard therapy alone [8].

A subsequent observational study (NCT06514976) evaluated the efficiency of Cytoflavin in patients with ischemic stroke not receiving reperfusion therapy. A randomized controlled trial (NCT05297851) evaluated Cytoflavin in patients with acute cerebral infarction who received reperfusion therapy (intravenous thrombolysis or mechanical thrombectomy), with Cytoflavin initiated within 24 hours of stroke onset as adjunctive neuroprotective therapy [2, 9].

The use of Cytoflavin during reperfusion in ischemic stroke has been reported to reduce the burden of reperfusion injury by attenuating oxidative stress and preserving mitochondrial function during the vulnerable post-reperfusion period. The effects of antioxidant treatment on neurotrophins and rehabilitation processes following stroke have been characterized, with Cytoflavin administration associated with increased serum brain-derived neurotrophic factor (BDNF) levels during the recovery period [26].

7.2 Chronic cerebral ischemia

Multicentre randomized studies of Cytoflavin tablets in patients with chronic cerebral ischemia (vascular cognitive impairment, chronic cerebrovascular insufficiency) demonstrated that oral Cytoflavin for 25 days reduced the clinical manifes-

tations of asthenia, anxiety, depression, cognitive impairment, and emotional disorders, with simultaneous improvement in quality-of-life measures [12]. The treatment effect was maintained at 30-day follow-up after treatment cessation.

7.3 Traumatic brain injury

The MITRA trial (NCT04631484), a multicenter, international, randomized, single-blind, placebo-controlled study, evaluated the efficacy and safety of Cytoflavin in the acute period of moderate traumatic brain injury in adults aged 18 to 60 years. Patients with non-penetrating TBI and Glasgow Coma Scale scores of 9 to 14 received Cytoflavin intravenously twice daily for 10 days, with treatment initiated within 24 hours of injury. Primary endpoints were the Galveston Orientation and Amnesia Test (GOAT) and the Glasgow Outcome Scale-Extended (GOS-E) assessed at day 90. The trial was conducted at centers in Russia and other countries and was completed in September 2024, with results published in *Frontiers in Neurology* in 2025 [1].

Earlier Russian studies had demonstrated the neuroprotective effect of Cytoflavin in closed craniocerebral trauma and the efficacy of the combination in the treatment of consequences of mild brain injury, where the drug produced more rapid improvement compared to aminaloni (gamma-aminobutyric acid) [27, 28].

7.4 Diabetic polyneuropathy (CYLINDER study)

The CYLINDER study (NCT04649203) is the most methodologically rigorous published trial of Cytoflavin. This multicenter, double-blind, placebo-controlled, randomized clinical trial enrolled 216 patients aged 45 to 74 years with type 2 diabetes mellitus and symptomatic distal sensorimotor diabetic polyneuropathy across 10 clinical centers. The treatment protocol was sequential: 10 days of intravenous Cytoflavin or placebo followed by 75 days of oral Cytoflavin or placebo tablets [10].

The primary endpoint was the change in Total Symptom Score (TSS), a validated patient-reported instrument measuring the severity of neuropathic symptoms (pain, burning, paresthesia, numbness). By the end of treatment, the TSS change in the experimental group was negative 2.65 points compared to negative 1.73 points in the placebo group (p less than 0.001), a statistically significant and clinically meaningful difference. Improvement in paresthesia and numbness components oc-

curred as early as day 11 of therapy (end of the intravenous phase). By the end of the full 85-day treatment course, a significant decrease in the burning component was also demonstrated [10].

A subgroup analysis demonstrated that improvement was achieved regardless of the degree of glycemic compensation (HbA1c level) but was greater in patients with less severe baseline symptoms (TSS less than 7.5 at baseline). The drug demonstrated a positive safety profile, with no serious adverse events and adverse event rates comparable to placebo [10].

7.5 Post-COVID-19 rehabilitation (CITADEL study)

The CITADEL prospective randomized study evaluated Cytoflavin in patients undergoing rehabilitation for post-COVID-19 syndrome. Patients were assessed using the Multidimensional Fatigue Inventory (MFI-20), the Mini-Mental State Examination (MMSE), the EQ-5D quality-of-life questionnaire, and the Pittsburgh Sleep Quality Index (PSQI). Cytoflavin administration achieved a pronounced anti-asthenic effect and correction of cognitive impairments, with significantly greater positive dynamics on all assessment scales compared to the comparator group receiving standard vitamins and nootropic drugs. The correction of mitochondrial dysfunction was proposed as the mechanistic basis for the observed clinical improvement in post-COVID asthenia [11, 29].

7.6 Postoperative cognitive decline

A clinical trial (NCT03849664) evaluated the efficacy and safety of Cytoflavin for the prevention of cognitive disorders after major surgery in elderly patients. Early studies had demonstrated the positive impact of perioperative Cytoflavin administration in preventing impairments of intelligence, speech, and attention after cardiac surgery. The ongoing trial aimed to extend these findings to non-cardiac major surgery in an elderly population [13].

7.7 Cognitive impairment in type 2 diabetes

A study evaluated the effectiveness of Cytoflavin for the correction of cognitive impairments in patients with type 2 diabetes mellitus, demonstrating improvement in cognitive function scores in the treatment group compared to controls. The mecha-

nism was attributed to the metabolic correction of cerebral energy failure associated with diabetic vasculopathy and to the neurotrophic effects of the individual components [14].

7.8 Organic asthenic disorder

Cytoflavin demonstrated improvement in symptoms of asthenia, emotional disorders, and autonomic dysregulation in patients with organic asthenic disorder in a published study. The asthenia endpoint is consistent across multiple indications (chronic cerebral ischemia, post-COVID syndrome, organic asthenic disorder) and likely reflects the correction of a common underlying metabolic substrate of central fatigue [30].

7.9 Elderly and senile patients

A recent study evaluated the effectiveness of Cytoflavin in the medical rehabilitation of elderly and senile patients, demonstrating improvement in functional and cognitive outcomes in this population. The metabolic mechanism is particularly relevant in aging, where mitochondrial dysfunction and NAD⁺ depletion are established contributors to cognitive decline and reduced functional capacity [31].

8. Sourcing and Quality Verification

Cytoflavin is a registered pharmaceutical product manufactured exclusively by POLYSAN Ltd. (Saint Petersburg, Russia) under GMP EU-certified conditions. The product is not a generic drug, a research chemical, or a dietary supplement; it is a registered medicinal product with standardized composition, manufacturing, and quality control.

Pharmaceutical-grade sourcing: Cytoflavin is available through Russian and CIS-region pharmacies by prescription. International procurement is available through licensed pharmaceutical export channels and through online pharmacies serving the Russian and CIS markets. The product is available in two formulations: enteric-coated tablets (50 or 100 tablets per pack) and concentrate for intravenous infusion (5 or 10 ampoules of 10 mL per pack) [4].

Quality verification for research applications: Investigators outside the Russian Federation and CIS region who obtain Cytoflavin for research purposes should consider the following quality verification steps:

- Confirmation of product authenticity through verification of batch numbers against POLYSAN records
- High-performance liquid chromatography quantitation of each active component against reference standards (succinic acid, inosine, nicotinamide, riboflavin)
- pH measurement of the injectable solution (expected range approximately 5.5 to 6.5)
- Visual inspection for particulates and color consistency (the injectable solution should be clear and yellow; the tablets should have intact enteric coating without chipping or discoloration)
- Verification of expiration date and storage conditions during transport

Individual component sourcing for research: Investigators conducting mechanistic studies or dose-finding research may prepare custom combinations from individual pharmaceutical-grade or research-grade components (succinic acid, inosine, nicotinamide, riboflavin) obtained from standard chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, others). All four components are commodity re-

search chemicals available in high purity (greater than 98 percent) at low cost. However, custom preparations do not replicate the specific formulation, buffering, and solubilization characteristics of the registered Cytoflavin product and should not be assumed to have equivalent pharmacokinetic or pharmacodynamic properties.

9. Reconstitution and Handling

9.1 Injectable formulation

The injectable formulation is supplied as a ready-to-use concentrate in sealed glass ampoules. Each 10 mL ampoule is diluted in 100 to 200 mL of carrier solution (0.9 percent sodium chloride or 5 to 10 percent dextrose) immediately before intravenous infusion. The diluted solution should be administered within 2 hours of preparation. The standard acute treatment course uses 10 to 20 mL (one to two ampoules) per infusion, administered twice daily [4].

Infusion rate: Not exceeding 4.3 mL per minute (approximately 90 drops per minute with a standard infusion set). Rapid administration may cause transient warmth, facial flushing, and mild tachycardia.

Compatibility: The injectable solution is compatible with 0.9 percent sodium chloride, 5 percent dextrose, and 10 percent dextrose as carrier solutions. Compatibility with other intravenous medications in the same infusion line has not been systematically characterized; admixture with other drugs is not recommended.

Storage: Store ampoules at 2 to 25 degrees Celsius, protected from light. Do not freeze. The yellow color of the solution is normal and reflects riboflavin content; solutions that have become deeply colored, turbid, or that contain visible particulates should be discarded.

9.2 Tablet formulation

The enteric-coated tablets are supplied in blister packs and should be stored at room temperature (15 to 25 degrees Celsius) in the original packaging, protected from moisture. The enteric coating prevents gastric irritation from succinic acid and should not be compromised by crushing or chewing.

Tablets should be taken at least 30 minutes before meals to optimize absorption. The recommended interval between the two daily doses is 8 to 10 hours. The evening dose should not be taken after 18:00 hours owing to the stimulatory metabolic effect of succinic acid, which may interfere with sleep onset [4].

9.3 Shelf life

The shelf life of the injectable formulation is typically 2 years from the date of manufacture when stored under recommended conditions. The shelf life of the tablet formulation is typically 2 years. Expired product should not be used.

10. Stack Interactions and Combinations

Cytoflavin is a combination of endogenous metabolites and vitamin cofactors that participate in fundamental cellular biochemistry. Drug interactions are generally limited to pharmacodynamic interactions related to the individual components and to the metabolic consequences of succinate and purine supplementation [4, 32].

Uric acid and gout medications: Inosine is catabolized to uric acid through xanthine oxidase. Concurrent administration with drugs that raise uric acid levels (thiazide diuretics, loop diuretics, pyrazinamide, ethambutol, low-dose aspirin) may produce additive hyperuricemia. Concurrent administration with xanthine oxidase inhibitors (allopurinol, febuxostat) may blunt the hyperuricemic effect of inosine but may also redirect purine metabolism toward the salvage pathway, potentially enhancing the ATP-resynthesis mechanism.

Hypoglycemic agents: Cytoflavin may produce transient hypoglycemia through activation of glucose utilization and intensification of aerobic glycolysis. Patients on insulin or sulfonylurea therapy should be monitored for hypoglycemia during the treatment course. The interaction is pharmacodynamic rather than pharmacokinetic [4].

Other succinate-based agents: Concurrent administration with Reamberin (meglumine sodium succinate) or Mexidol (ethylmethylhydroxypyridine succinate) provides redundant succinate supplementation and is pharmacologically unnecessary. The combination has not been associated with safety concerns but is not recommended owing to the absence of expected additional benefit.

Levodopa: Riboflavin may theoretically reduce the efficacy of levodopa by accelerating its peripheral metabolism through enhanced activity of riboflavin-dependent aromatic amino acid decarboxylase. This interaction is theoretical and has not been documented clinically at the riboflavin doses present in Cytoflavin.

Monoamine oxidase inhibitors: Riboflavin is a precursor to FAD, the prosthetic group of monoamine oxidase A and B. Supplementation could theoretically enhance monoamine oxidase activity, though the effect at Cytoflavin doses (5 to 20 mg

riboflavin per day) is not clinically significant.

Anticoagulants and antiplatelet agents: No pharmacokinetic or pharmacodynamic interactions have been characterized between Cytoflavin and anticoagulants or antiplatelet agents. Concurrent use in stroke and TBI patients is standard practice in the published clinical studies.

Cholinesterase inhibitors: Concurrent use with donepezil, rivastigmine, or galantamine for cognitive indications has not been studied but is expected to be safe, as the mechanisms are complementary (metabolic support versus cholinergic enhancement).

Other neuroprotective agents: Concurrent use with Cerebrolysin, citicoline, or Actovegin has been employed in clinical practice in the Russian Federation and CIS region. Published pharmacoeconomic analyses have compared these agents as alternatives rather than as combinations, and combination pharmacology data are limited [33].

11. Adverse Events and Safety

11.1 Common adverse events

The safety profile of Cytoflavin across published clinical studies is favorable. The principal adverse events reported in the tablet formulation prescribing information and in clinical trials are [4, 10, 11]:

- Epigastric discomfort, nausea, or pain (uncommon; attributable to succinic acid, mitigated by enteric coating and pre-meal administration)
- Headache (uncommon)
- Hyperuricemia (common at the population level; attributable to inosine-derived purine catabolism via xanthine oxidase; typically asymptomatic but relevant in patients with pre-existing hyperuricemia or gout)
- Transient hypoglycemia (uncommon; attributable to enhanced glucose utilization)
- Exacerbation of gout (rare; attributable to hyperuricemia)
- Hypersensitivity reactions including skin hyperemia and pruritus (rare)

11.2 Adverse events specific to the injectable formulation

The injectable formulation has additional adverse events related to the intravenous route and to the rapid delivery of metabolic substrates [4]:

- Feeling of warmth or heat (uncommon; related to succinate-driven metabolic activation and to meglumine buffering)
- Transient facial flushing (uncommon)
- Chills (rare)
- Weakness and sweating (rare)
- Pain and redness at the injection site or along the vein (uncommon)

These adverse events are typically transient and resolve without intervention. Reduction of the infusion rate mitigates most infusion-related reactions.

11.3 Serious adverse events

No serious adverse events attributable to Cytoflavin have been reported in published controlled clinical trials, including the CYLINDER study (216 patients), the CITADEL study, the MITRA trial, and the multicenter stroke studies. The absence of serious adverse events is consistent with the pharmacological profile of the four components, all of which are endogenous metabolites and vitamin cofactors with established safety at the administered doses [1, 10, 11].

11.4 Overdose

No cases of Cytoflavin overdose have been identified in the published literature or in postmarketing surveillance. The individual components have well-characterized toxicology at suprapharmacological doses: succinic acid has very low acute toxicity (oral LD50 in rats greater than 2 g/kg); inosine toxicity is limited to hyperuricemia; nicotinamide at very high doses (greater than 3 g/day) can cause hepatotoxicity; and riboflavin has no established toxicity at any oral dose owing to saturable intestinal absorption [4].

11.5 Contraindications

The prescribing information lists the following contraindications: known hypersensitivity to any component; pregnancy and lactation (insufficient safety data); children under 18 years (insufficient pediatric data for the combination product, though individual components are used in pediatric populations). Relative contraindications include nephrolithiasis (uric acid stones), gout, and severe renal impairment [4].

11.6 Pregnancy and lactation

Human pregnancy data for the Cytoflavin combination product are not available. The individual components (succinic acid, inosine, nicotinamide, riboflavin) are endogenous metabolites and vitamins present in normal pregnancy and are not teratogenic at dietary or supplemental doses. However, the pharmacological doses used in Cytoflavin exceed normal dietary intake, and the combination has not been studied in pregnancy. The prescribing information recommends against use in pregnancy and lactation unless clearly indicated.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative neuroprotective and metabolic agents against Cytoflavin, 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 the principal metabolic and neuroprotective agents used in overlapping clinical indications (ischemic stroke, chronic cerebral ischemia, traumatic brain injury, cognitive impairment) with emphasis on agents available in the same markets or studied in the same patient populations as Cytoflavin.

12.1 Mexidol (ethylmethylhydroxypyridine succinate)

Mechanism: Mexidol is a synthetic succinic acid derivative (the 2-ethyl-6-methyl-3-hydroxypyridine salt of succinic acid) that combines the succinate-mediated anti-hypoxant activity with a 3-hydroxypyridine antioxidant moiety. The 3-hydroxypyridine component provides direct free radical scavenging and membrane-stabilizing activity; the succinate component provides the same Complex II substrate activity as the succinic acid in Cytoflavin [34].

Development trajectory: Mexidol was developed in Russia and is registered in the Russian Federation and CIS countries for treatment of acute ischemic stroke, chronic cerebral ischemia, anxiety disorders, and alcohol withdrawal syndrome. It has been studied in multiple Russian multicenter trials and is one of the most prescribed neuroprotective agents in the Russian Federation.

Novelty: Moderate. The 3-hydroxypyridine moiety provides a synthetic antioxidant component absent from endogenous metabolite combinations. However, the overall pharmacological concept (succinate delivery plus antioxidant support) is shared with Cytoflavin.

Effect size: In a pharmacoeconomic analysis comparing Mexidol, Cytoflavin, and Actovegin for mild ischemic stroke, the three agents showed similar efficacy, with mean improvement differences of 0.2 for Mexidol compared to 0.61 for Cytoflavin

[33]. The difference suggests a modest advantage for Cytoflavin in this specific comparison, though the study was not a head-to-head randomized controlled trial.

Promising potential: Moderate. Mexidol has a large clinical evidence base in Russian-language literature and a strong market position in Russia. International development and English-language evidence are limited. The compound is not registered outside Russia and the CIS.

Side-effect profile: Generally well tolerated. Adverse events include nausea, dry mouth, somnolence, and allergic reactions. The profile is broadly comparable to Cytoflavin.

Overall validation: Moderate. Extensive Russian clinical evidence; limited international evidence. No major Western regulatory registration.

Comparison to Cytoflavin: Mexidol provides succinate plus synthetic antioxidant; Cytoflavin provides succinate plus three additional metabolic cofactors (inosine, nicotinamide, riboflavin). Cytoflavin has the broader metabolic coverage and the more rigorous recent international trial evidence (CYLINDER, MITRA). Mexidol has the longer market history in Russia and the larger overall Russian clinical literature.

12.2 Actovegin (deproteinized hemodialysate of calf blood)

Mechanism: Actovegin is a deproteinized hemodialysate derived from calf blood, containing a heterogeneous mixture of low-molecular-weight peptides, amino acids, nucleosides, oligosaccharides, and inorganic electrolytes. The proposed mechanism is enhancement of cellular glucose and oxygen uptake, stimulation of oxidative metabolism, and insulin-like activity through activation of the insulin signaling pathway independently of the insulin receptor [35].

Development trajectory: Actovegin has been used in Europe (particularly Germany, Austria, and Eastern Europe) and in Russia for decades in indications including diabetic polyneuropathy, peripheral arterial disease, cerebral ischemia, and wound healing. The landmark ARTEMIDA trial (randomized, double-blind, placebo-controlled, 503 patients) evaluated Actovegin in post-stroke cognitive impairment and reported significant improvement on the Montreal Cognitive Assessment at 6 months [35].

Novelty: Low. The product is a biological extract with incompletely characterized active principles. The mechanism is not precisely defined at the molecular level.

Effect size: The ARTEMIDA trial reported statistically significant cognitive improvement in post-stroke patients. In the pharmacoeconomic comparison with Cytoflavin and Mexidol, Actovegin showed an improvement of 0.2, similar to Mexidol and lower than the 0.61 for Cytoflavin [33]. The diabetic polyneuropathy literature shows effect sizes comparable to alpha-lipoic acid.

Promising potential: Moderate. The product has a long clinical history and is registered in multiple countries. However, regulatory scrutiny of biological extracts has increased, and the product is not approved by the FDA. The incompletely defined mechanism limits acceptance in evidence-based pharmacology.

Side-effect profile: Generally well tolerated. Rare hypersensitivity reactions including anaphylaxis have been reported (the product is derived from animal blood). The biological origin raises theoretical concerns about transmissible agents, though processing steps are designed to eliminate this risk.

Overall validation: Moderate to high. Extensive clinical use over decades; the ARTEMIDA trial provides rigorous evidence for one indication. The biological-extract nature limits mechanistic precision.

Comparison to Cytoflavin: Actovegin is a biological extract with incompletely defined mechanism; Cytoflavin is a chemically defined combination of known metabolites with characterized molecular targets. Cytoflavin has the advantage of precise mechanistic rationale and reproducible composition. Actovegin has the advantage of a longer international clinical history and a larger Western evidence base (the ARTEMIDA trial).

12.3 Cerebrolysin (porcine brain-derived peptide preparation)

Mechanism: Cerebrolysin is a brain-derived peptidergic mixture obtained by enzymatic hydrolysis of purified porcine brain protein. The preparation contains neurotrophic peptides that mimic the activities of endogenous neurotrophic factors

(nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor) and that activate neuronal survival, differentiation, and synaptic plasticity signaling pathways including PI3K/Akt, MAPK/ERK, and JAK/STAT [36].

Development trajectory: Cerebrolysin has been studied in multiple large randomized controlled trials for acute ischemic stroke, traumatic brain injury, and Alzheimer's disease. The CAPTAIN and CAPTAIN II trials evaluated Cerebrolysin in TBI. A meta-analysis of 14 randomized controlled trials found that Cerebrolysin significantly improved neurological recovery in acute ischemic stroke (mean difference in NIHSS change of 1.39 points favoring Cerebrolysin). The product is registered in over 40 countries but is not approved by the FDA [36].

Novelty: Low to moderate. The neurotrophic peptide mechanism is distinct from the metabolic mechanism of Cytoflavin. The product has been available for over 40 years.

Effect size: Meta-analytic evidence supports a small but statistically significant effect on neurological recovery in acute ischemic stroke. TBI evidence is mixed. Alzheimer's disease trials have produced inconsistent results.

Promising potential: Moderate. Large international evidence base and widespread registration. Active clinical development continues. The biological-extract nature (like Actovegin) limits acceptance in some regulatory environments.

Side-effect profile: Generally well tolerated. Adverse events include headache, dizziness, agitation, and injection-site reactions. Rare hypersensitivity reactions. The safety profile in meta-analysis is comparable to placebo.

Overall validation: Moderate to high. The most extensively studied neuroprotective peptide preparation, with meta-analytic evidence across multiple indications. The lack of FDA approval and the biological-extract nature are limitations.

Comparison to Cytoflavin: Cerebrolysin acts through neurotrophic peptide signaling; Cytoflavin acts through metabolic substrate and cofactor provision. The mechanisms are complementary rather than overlapping. Cerebrolysin has the larger international evidence base and broader regulatory registration. Cytoflavin has the advantage of defined composition, oral availability, and lower cost per treatment course.

12.4 Citicoline (CDP-choline, cytidine-5'-diphosphocholine)

Mechanism: Citicoline is an endogenous nucleotide that serves as an intermediate in the biosynthesis of phosphatidylcholine, the principal phospholipid of cell membranes. Exogenous citicoline provides cytidine (a precursor to uridine and subsequently to UTP, CTP, and nucleic acids) and choline (a precursor to phosphatidylcholine and to acetylcholine). The mechanism includes membrane repair, cholinergic neurotransmission support, and preservation of cardiolipin (the inner mitochondrial membrane phospholipid required for electron transport chain complex assembly) [37].

Development trajectory: Citicoline has been studied extensively in acute ischemic stroke, traumatic brain injury, and cognitive impairment. The ICTUS trial, a large multicenter randomized double-blind placebo-controlled trial of citicoline in acute ischemic stroke (2298 patients), did not demonstrate significant benefit on the primary outcome (global recovery at 90 days). Despite this negative result, citicoline is registered in many countries (predominantly in Europe, Asia, and Latin America) as a neuroprotective agent and is available as a dietary supplement in the United States [37].

Novelty: Low. Citicoline has been studied for over 40 years and the mechanism is well established.

Effect size: The ICTUS trial was negative for the primary endpoint. Earlier, smaller trials had suggested benefit. Meta-analyses have produced mixed results. Effect sizes, when positive, are small.

Promising potential: Low to moderate. The negative ICTUS trial substantially reduced enthusiasm for citicoline as a single-agent neuroprotective intervention in acute stroke. The compound remains widely used in clinical practice in many countries. Research continues in TBI and cognitive impairment.

Side-effect profile: Excellent. Citicoline is extremely well tolerated with adverse event rates comparable to placebo in large trials. Rare gastrointestinal effects (nausea, diarrhea) and headache.

Overall validation: Moderate. Extensive clinical literature over four decades, but the pivotal ICTUS trial was negative. The safety profile is excellent.

Comparison to Cytoflavin: Citicoline acts through membrane phospholipid biosynthesis and cholinergic support; Cytoflavin acts through mitochondrial metabolic rescue. The mechanisms are complementary. Citicoline has the larger international evidence base and broader regulatory acceptance. Cytoflavin has positive controlled trial evidence (CYLINDER) that citicoline lacks in its pivotal stroke trial. The safety profiles of both compounds are excellent.

12.5 Reamberin (meglumine sodium succinate)

Mechanism: Reamberin is an isotonic detoxification and antihypoxant infusion solution containing meglumine sodium succinate as the principal active ingredient, with sodium chloride, potassium chloride, and magnesium chloride as electrolyte components. The mechanism is succinate delivery to Complex II, identical to the succinic acid component of Cytoflavin. Reamberin is manufactured by the same company (POLYSAN Ltd.) that manufactures Cytoflavin [15].

Development trajectory: Reamberin is registered in the Russian Federation for detoxification therapy in various intoxications, for hepatoprotection, and for antihypoxant support in critical care. Clinical evidence is predominantly in Russian-language journals.

Novelty: Low. The mechanism is a single-component version of one element of the Cytoflavin combination.

Effect size: Clinical evidence for Reamberin is predominantly in detoxification and hepatoprotective indications rather than in the neurological indications where Cytoflavin has its evidence base. Direct comparison of effect sizes is difficult owing to different indication populations.

Promising potential: Low. The compound is principally a critical-care supportive agent and is not positioned for the neurological and cognitive indications where Cytoflavin is studied.

Side-effect profile: Well tolerated. Infusion-related reactions (warmth, flushing) are similar to Cytoflavin injectable formulation. The electrolyte content requires monitoring of serum electrolytes during prolonged infusion.

Overall validation: Low to moderate. Established in Russian critical care; minimal international evidence.

Comparison to Cytoflavin: Reamberin provides succinate only; Cytoflavin provides succinate plus inosine, nicotinamide, and riboflavin. The Cytoflavin formulation is a superset of the Reamberin mechanism with additional cofactor and nucleoside support. For neurological indications, Cytoflavin has a substantially larger and more rigorous evidence base. Reamberin is positioned differently (detoxification, critical care) and is not a direct alternative in neurological applications.

12.6 Comparator summary

The five comparators occupy distinct positions in the neuroprotective and metabolic pharmacology landscape. **Mexidol** is the closest mechanistic relative, providing succinate plus synthetic antioxidant; it lacks the cofactor and nucleoside components of Cytoflavin and has less rigorous international trial evidence. **Actovegin** is a biological extract with long clinical history but imprecise mechanism; it occupies the same clinical niche but with less mechanistic transparency. **Cerebrolysin** acts through a fundamentally different mechanism (neurotrophic peptides) and has the strongest international evidence base among the comparators; it is complementary rather than competitive with Cytoflavin. **Citicoline** acts through membrane phospholipid biosynthesis and has extensive international evidence but a negative pivotal stroke trial; its safety profile is the benchmark for the class. **Reamberin** is a single-component succinate-delivery vehicle from the same manufacturer; it is mechanistically a subset of Cytoflavin.

Cytoflavin occupies a unique position in this comparator landscape: it is the only product with a chemically defined four-component metabolic rescue mechanism, the only product with a positive pivotal placebo-controlled trial in diabetic polyneuropathy (the CYLINDER study), and the only product with an expanding international clinical trial program including registered trials on ClinicalTrials.gov across multiple neurological indications. Its principal limitations are the predominantly Russian-language evidence base, the absence of major Western regulatory registration, and the biological origin of its therapeutic rationale in the Russian metabolic pharmacology tradition, which is less familiar to Western clinical investigators.

The principal practical question for the research positioning of Cytoflavin is whether the combination metabolic mechanism, which addresses multiple simultaneous bottlenecks in mitochondrial energy failure, produces clinically meaningful additive or synergistic benefit compared to single-agent interventions. The

CYLINDER study provides the strongest evidence that the combination approach produces measurable clinical benefit. The pharmacoeconomic comparison suggesting greater efficacy than Mexidol and Actovegin in mild ischemic stroke provides supportive, though not definitive, evidence. The ongoing and recently completed international trials (MITRA, NCT05297851, NCT05935787) will provide additional data points for this assessment.

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