

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Retinalamin

*A tissue-derived polypeptide fraction developed at the St. Petersburg Institute of Bioregulation and Gerontology as a retinoprotective agent, distinguished from conventional neuroprotective ophthalmologics by its multi-peptide composition, tissue-specific gene expression regulation, and clinical application across glaucoma, diabetic retinopathy, and hereditary retinal dystrophies.*

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## ABSTRACT

Retinalamin is a complex of water-soluble polypeptide fractions with molecular weight not exceeding 10,000 daltons, isolated from bovine retinal tissue and developed as a retinoprotective peptide bioregulator by Vladimir Khavinson and colleagues at the St. Petersburg Institute of Bioregulation and Gerontology of the Russian Academy of Medical Sciences. The compound is registered in the Russian Federation and several Commonwealth of Independent States jurisdictions as a lyophilized preparation for parabulbar and intramuscular injection, manufactured by Geropharm LLC under the ATC code S01XA (other preparations for eye disease treatment). Retinalamin represents a distinct pharmacological class within ophthalmic neuroprotection: rather than a single molecular entity with a defined receptor target, it consists of a heterogeneous mixture of short-chain polypeptides (predominantly 2 to 7 amino acid residues in length) that act through tissue-specific modulation of gene expression, stimulation of intracellular protein synthesis, regulation of lipid peroxidation, and normalization of cellular membrane function in retinal photoreceptors, retinal pigment epithelium, and Mueller glial cells.

The mechanistic basis of Retinalamin activity has been characterized through in vitro and in vivo models at the St. Petersburg Institute. In *Xenopus laevis* early gastrula ectoderm assays, Retinalamin demonstrated concentration-dependent induction of neuronal differentiation including brain, retinal, and pigment epithelium lineages, establishing the compound as a morphogenetic peptide regulator with tissue-specific inductive

capacity. In cell culture, Retinalamin and the related synthetic tetrapeptide Epithalon stimulated proliferation of retinal and pigmented epithelial cells in a tissue-specific and concentration-dependent manner. The proposed molecular mechanism involves sequential binding of constituent short peptides to promoter regions of genes involved in retinal cell differentiation, survival, and metabolic homeostasis, thereby modulating transcriptional activity and downstream protein expression. Pharmacodynamic effects observed in preclinical and clinical settings include stimulation of photoreceptor and retinal cellular element function, improvement of functional interactions between retinal pigment epithelium and photoreceptor outer segments, enhancement of Mueller cell activity and glutamate inactivation, normalization of vascular permeability, and reduction of oxidative stress through regulation of lipid peroxide metabolism.

Clinical evidence for Retinalamin spans multiple retinal pathologies. In compensated primary open-angle glaucoma, a 180-patient randomized controlled trial (Egorov et al. 2019) demonstrated that intramuscular Retinalamin produced significant retinoprotective effects, with improvement in mean deviation index from negative 5.52 to negative 4.82 decibels, stabilization of ganglion cell complex thickness (versus progressive thinning in controls), and preservation of pattern electroretinography amplitudes over the study period. A subsequent 147-patient randomized trial (Strakhov et al. 2020) demonstrated that biannual Retinalamin courses over 24 months arrested development of glaucomatous optic neuropathy, with retinal nerve fiber layer thickness remaining stable in treated patients versus declining from 83.5 to 76.7 micrometers in controls. In diabetic retinopathy, a 56-patient comparative study (Malakhova et al. 2024) provided objective structural and

functional evidence of positive retinal changes with intramuscular Retinalamin in early-stage disease. In hereditary retinal dystrophies, long-term observational data (Razumovskiy et al.) demonstrated that a first course of Retinalamin improved visual acuity in 58.1 percent and visual fields in 64.5 percent of retinal degeneration patients, with repeated courses over 23 to 25 years preserving residual vision in 55.6 percent of patients and preserving object vision in 11.1 percent. In retinal abiotrophy, residual vision was preserved in 100 percent of treated cases. A 498-patient glaucoma study (Erichiev et al. 2020) comparing intramuscular, retrobulbar, and combined administration routes demonstrated comparable efficacy across delivery methods, with total threshold retinal sensitivity increasing by 122 to 274 decibels across glaucoma stages.

The safety profile of Retinalamin is characterized by low adverse event rates. The principal reported events are local injection site reactions (pain, redness, swelling) and rare hypersensitivity reactions including anaphylactic shock and angioneurotic laryngeal edema. The compound is contraindicated during pregnancy (absence of clinical safety data) and in pediatric populations under 18 years for most indications. Pharmacokinetic characterization in the conventional sense is not feasible owing to the multi-component polypeptide composition, which does not permit standard absorption, distribution, metabolism, and elimination analysis of individual constituents. The standard clinical regimen consists of 5 to 10 milligrams administered once daily by parabolbar or intramuscular injection for 5 to 10 days, with courses repeated every 3 to 6 months. Retinalamin is not approved by the United States Food and Drug Administration, the European Medicines Agency, or other major Western regulatory authorities. The clinical evidence base is derived predominantly

from Russian-language literature published in Vestnik Oftalmologii and related journals. Investigators outside the Russian Federation should approach the compound as a research-grade peptide preparation requiring independent analytical verification and should interpret the clinical literature with attention to the methodological standards and reporting conventions of the source publications.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name (proposed):** Polypeptides of cattle retina.

**Marketed name:** Retinalamin (Geropharm LLC, Russian Federation). The compound is also referred to in the scientific literature as retinalamine (the transliterated Russian form) and as retinal peptide bioregulator.

**Development origin:** St. Petersburg Institute of Bioregulation and Gerontology, Northwestern Division of the Russian Academy of Medical Sciences. The compound was developed under the direction of Vladimir Khavinson as part of a broader peptide bioregulator program that includes Cortexin (brain-derived peptides), Thymalin (thymus-derived peptides), Epithalamin (pineal-derived peptides), and other tissue-specific polypeptide preparations [1, 2].

**ATC classification code:** S01XA (other preparations for eye disease treatment).

**Chemical Abstracts Service registry number:** No single CAS number is assigned. Retinalamin is a multi-component biological extract, not a single chemical entity, and is therefore not registered in chemical databases as a defined molecular species.

**Pharmacological group:** Tissue regeneration stimulator; polypeptide bioregulator.

## 1.2 Structural class and chemistry

Retinalamin is not a single compound with a defined molecular structure. It is a complex of water-soluble polypeptide fractions with molecular weight not exceeding 10,000 daltons, isolated from the retinal tissue of cattle (*Bos taurus*) by acid extraction and subsequent ultrafiltration [3]. The polypeptide fractions consist predominantly of short peptides in the range of 2 to 7 amino acid residues, consistent with the Khavinson peptide bioregulator paradigm in which tissue-specific regulatory function is attributed to oligopeptides that interact with gene promoter regions in a sequence-specific manner [1].

**Molecular formula:** Not applicable (multi-component biological extract).

**Molecular weight range:** Less than 10,000 daltons (upper limit of the ultrafiltration cutoff).

**Physical form:** White to off-white lyophilized powder. Each commercial vial contains 5 milligrams of Retinalamin polypeptide fraction and 17 milligrams of glycine as stabilizer [4, 5].

**Solubility:** Freely soluble in water and in 0.9 percent sodium chloride solution. Soluble in 0.5 percent procaine (novocaine) solution for injection.

The amino acid composition of the polypeptide mixture has been characterized by the St. Petersburg Institute but full sequence identification of all constituent peptides has not been published in the peer-reviewed literature. The synthetic tetrapeptide Epithalon (Ala-Glu-Asp-Gly), which shares functional properties with certain Retinalamin fractions in stimulating retinal and pigmented epithelial cell proliferation, has been identified as a structurally related reference compound [6].

## 1.3 Manufacture and extraction

Retinalamin is manufactured by Geropharm LLC (Russian Federation) using a patented extraction technology developed at the St. Petersburg Institute of Bioregulation and Gerontology [4]. The manufacturing process involves acid extraction of polypeptide fractions from bovine retinal tissue, followed by ultrafiltration to retain only fractions below 10,000 daltons, purification, lyophilization with glycine stabilizer, and aseptic filling into glass vials. The manufacturing process is subject to Russian Federation Good Manufacturing Practice standards. Geropharm is the sole authorized manufacturer of the branded Retinalamin preparation.

Quality control parameters include peptide content determination, amino acid composition analysis, sterility testing, bacterial endotoxin testing, and stability assessment. The compound is supplied as a lyophilisate for reconstitution in 5 milligram vials (10 vials per package) [5].

## 2. Abstract

Retinalamin is a polypeptide bioregulator preparation derived from bovine retinal tissue, consisting of a heterogeneous mixture of water-soluble peptide fractions with molecular weight below 10,000 daltons. Developed by Vladimir Khavinson and colleagues at the St. Petersburg Institute of Bioregulation and Gerontology as part of a systematic program of tissue-specific peptide bioregulator development, Retinalamin is registered in the Russian Federation and several CIS jurisdictions for the treatment of compensated primary open-angle glaucoma, diabetic retinopathy, central retinal dystrophy of inflammatory and traumatic origin, tapetoretinal abiotrophy, and myopic disease [4, 5].

The compound occupies a unique position in ophthalmic pharmacology as a multi-peptide biological extract that acts through gene expression modulation rather than through a single defined receptor interaction. The mechanistic paradigm, established through the broader Khavinson peptide bioregulator research program, proposes that short oligopeptides (2 to 7 amino acids) interact with specific DNA sequences in gene promoter regions, modulating transcription of genes involved in cell differentiation, proliferation, and metabolic homeostasis in a tissue-specific manner [1, 2]. For Retinalamin specifically, preclinical studies have demonstrated concentration-dependent induction of neuronal differentiation in *Xenopus laevis* ectodermal explants, tissue-specific stimulation of retinal and pigmented epithelial cell proliferation in culture, and pharmacodynamic effects including enhancement of photoreceptor function, normalization of retinal pigment epithelium and photoreceptor interactions, stimulation of Mueller cell activity, and reduction of oxidative stress [7, 8].

The clinical evidence base spans several retinal pathologies, with the most substantive data in open-angle glaucoma and hereditary retinal dystrophies. Randomized controlled trials in glaucoma have demonstrated retinoprotective effects including stabilization of retinal nerve fiber layer thickness, improvement in visual field mean deviation, and preservation of pattern electroretinography amplitudes [9, 10, 11]. Long-term observational studies in retinal dystrophies have reported vision improvement in the majority of patients after initial treatment cour-

ses and preservation of residual vision with sustained biannual treatment over decades [12]. The safety profile is favorable, with adverse events limited predominantly to local injection site reactions and rare systemic hypersensitivity [4, 5].

Retinalamin is not approved outside the Russian Federation and CIS jurisdictions. The clinical literature is predominantly Russian-language, published in *Vestnik Oftalmologii* and related journals, and the methodological standards of the published trials vary. The compound has not been evaluated in large-scale, multicenter, double-masked, placebo-controlled trials conforming to International Council for Harmonisation guidelines. A 2021 experimental study in a rabbit photochemical retinal damage model did not find significant functional or morphological evidence of neuroprotective effects, highlighting the need for rigorous independent replication of the clinical findings [13]. Investigators considering Retinalamin for research applications should approach it as a biologically active polypeptide preparation with a substantial but geographically concentrated clinical literature and should obtain independent analytical characterization of any acquired material.

## 3. Discovery and Development History

### 3.1 Origin and the peptide bioregulator paradigm

Retinalamin was developed within the broader peptide bioregulator research program initiated by Vladimir Khavinson at the Military Medical Academy and subsequently at the St. Petersburg Institute of Bioregulation and Gerontology, beginning in the 1970s and 1980s [1]. The foundational concept of this program is that short peptides (2 to 7 amino acids) extracted from specific tissues carry regulatory information that modulates gene expression in a tissue-specific manner, and that administration of these peptides to homologous tissues can restore declining function associated with aging, disease, or injury. The program produced a series of tissue-derived polypeptide preparations: Thymalin (thymus), Epithalamin (pineal gland), Cortexin (brain cortex), Prostatilen (prostate), and Retinalamin (retina), among others [2].

### 3.2 Development of Retinalamin

Retinalamin was developed specifically for retinal pathology by extraction and purification of polypeptide fractions from bovine retinal tissue. The original extraction and purification protocol was developed at the St. Petersburg Institute and subsequently transferred to Geropharm LLC for commercial manufacture. The compound received registration in the Russian Federation as a medicinal product under the pharmacological classification of tissue regeneration stimulators [4].

### 3.3 Preclinical characterization

The preclinical characterization of Retinalamin was conducted principally at the St. Petersburg Institute of Bioregulation and Gerontology. Khavinson, Malinin, Trofimova, and Zemchikhina (2002) demonstrated that Retinalamin exhibited inductive activity on multipotent ectodermal cells of *Xenopus laevis* early gastrula, with neuronal differentiation (including brain, retina, and pigment epithelium lineages) depending on Retinalamin concentration [7]. This study established the morphogenetic capacity of the retinal peptide preparation and supported the tissue-specificity paradigm central to the broader bioregulator program.

Khavinson, Zemchikhina, Trofimova, and Malinin (2003) extended the characterization to demonstrate that Retinalamin and the synthetic tetrapeptide Epithalon (Ala-Glu-Asp-Gly) stimulated proliferation of retinal and pigmented epithelial cells in culture in a tissue-specific and concentration-dependent manner [8]. The tissue specificity observation (activity on retinal and pigment epithelial cells but not on unrelated cell types at the same concentrations) was interpreted as supporting the hypothesis that the constituent peptides interact with cell-type-specific gene regulatory elements.

### 3.4 Clinical development and registration

Retinalamin progressed through clinical evaluation in Russian ophthalmological centers, principally at institutions in St. Petersburg, Moscow, and Yaroslavl. The clinical development followed the Russian regulatory pathway for biological medicinal products and resulted in registration for multiple retinal indications including compensated primary open-angle glaucoma, diabetic retinopathy, central retinal dystrophies, tapetoretinal abiotrophy, and myopic disease [4, 5]. The compound has been in clinical use in the Russian Federation for over two decades, with an expanding clinical evidence base published primarily in *Vestnik Oftalmologii* (Bulletin of Ophthalmology) and other Russian-language ophthalmological journals.

### 3.5 International status

Retinalamin has not been submitted for regulatory approval to the United States Food and Drug Administration, the European Medicines Agency, or other major Western regulatory agencies. The compound is available internationally through Russian pharmaceutical exporters and online peptide vendors, typically marketed as a research-grade or health supplement preparation rather than as a registered medicine. The absence of international regulatory approval reflects both the nature of the compound (a multi-component biological extract that does not conform to the single-entity paradigm of Western drug regulation) and the geographic concentration of the clinical development program.

## 4. Mechanism of Action

### 4.1 Gene expression regulation by short peptides

The mechanistic paradigm for Retinalamin derives from the broader Khavinson peptide bioregulator hypothesis, which proposes that short oligopeptides (2 to 7 amino acids) interact directly with DNA at specific sequences within gene promoter regions, modulating transcriptional activity in a tissue-specific manner [1, 2]. According to this model, the constituent peptides of Retinalamin bind to complementary DNA sequences through hydrogen bonding and electrostatic interactions, facilitating or inhibiting the binding of transcription factors and thereby regulating the expression of genes involved in retinal cell differentiation, survival, and metabolic function.

Experimental support for the gene-regulatory mechanism comes from studies demonstrating that Khavinson peptides (including the Retinalamin-related tetrapeptide Epithalon) can penetrate cell nuclei, interact with histones and DNA, and alter gene expression patterns in cultured cells [1]. The specific promoter targets and gene expression changes induced by the individual peptide components of Retinalamin have not been comprehensively mapped, and the mechanistic model remains at a level of generality that does not permit precise molecular pharmacological characterization comparable to that available for single-entity receptor ligands.

### 4.2 Retinal cell differentiation and proliferation

In *Xenopus laevis* early gastrula ectodermal explant assays, Retinalamin induced concentration-dependent neuronal differentiation, with morphological and immunohistochemical evidence of differentiation into brain, retinal, and pigment epithelium lineages [7]. This morphogenetic activity establishes Retinalamin as a peptide preparation with inductive capacity on multipotent neuroectodermal cells, consistent with the hypothesis that the constituent peptides carry tissue-specific developmental regulatory information.

In cell culture studies, Retinalamin stimulated proliferation of retinal cells and pigmented epithelial cells in a concentration-dependent and tissue-specific manner [8]. The synthetic tetrapeptide Epithalon (Ala-Glu-Asp-Gly) produced similar tissue-specific stimulatory effects, supporting the interpretation that defined short peptide sequences within the Retinalamin mixture are responsible for the observed biological activity.

## 4.3 Pharmacodynamic effects on retinal tissue

The pharmacodynamic effects of Retinalamin, as characterized in preclinical models and inferred from clinical observations, include the following [4, 5, 14]:

**Stimulation of photoreceptor function.** Retinalamin enhances the functional activity of rod and cone photoreceptors, as measured by electroretinographic amplitude increases in both preclinical and clinical settings.

**Improvement of retinal pigment epithelium and photoreceptor interactions.** The compound normalizes the functional relationship between the retinal pigment epithelium monolayer and the photoreceptor outer segments, supporting the phagocytic, metabolic, and structural support functions of the pigment epithelium.

**Enhancement of Mueller cell activity and glutamate inactivation.** Retinalamin stimulates Mueller glial cell function, including the glutamate-glutamine shuttle that is critical for maintaining appropriate glutamate concentrations in the retinal extracellular space. Excessive extracellular glutamate is excitotoxic to retinal ganglion cells and photoreceptors; enhancement of Mueller cell glutamate uptake and conversion is therefore neuroprotective.

**Regulation of lipid peroxidation and oxidative stress.** The compound reduces lipid peroxide accumulation in retinal tissue, an effect attributed to upregulation of endogenous antioxidant enzyme systems rather than to direct free-radical scavenging by the peptide components.

**Normalization of vascular permeability.** In diabetic retinopathy and other conditions characterized by breakdown of the blood-retinal barrier, Retinalamin has been reported to reduce vascular permeability and normalize retinal microcirculation.

Normalization of cellular membrane function. The compound stabilizes retinal cell membrane integrity and function, supporting ion channel activity, receptor density, and membrane-associated enzyme systems.

## 4.4 Anti-apoptotic and neuroprotective mechanisms

The neuroprotective effects of Retinalamin are attributed to a combination of anti-apoptotic signaling, neurotrophic factor modulation, and reduction of excitotoxicity [14]. The specific molecular pathways (e.g., Bcl-2 family regulation, caspase cascade modulation, PI3K/Akt signaling) through which these effects are mediated have not been comprehensively characterized for Retinalamin itself, though related Khavinson peptides (notably Epithalon) have been shown to prevent apoptosis in retinal pigment epithelium cells and to stimulate regenerative processes in aging retinal tissue [1].

It should be noted that a 2021 experimental study by Suetov et al., employing a rabbit model of photochemical retinal damage with 405-nanometer light exposure, did not find significant functional or morphological evidence of neuroprotective effects of Retinalamin administered by parabulbar injection at 0.25 mg/kg over 10 days [13]. This negative finding in a controlled animal model contrasts with the positive clinical observations and highlights the importance of model selection, dosing protocol, and endpoint sensitivity in evaluating the retinoprotective activity of the compound.

## 4.5 Limitations of mechanistic characterization

The mechanistic understanding of Retinalamin is limited by several factors inherent to multi-component biological extracts. The heterogeneous composition prevents attribution of observed effects to individual molecular species. The proposed gene-regulatory mechanism, while supported by indirect evidence from the broader Khavinson peptide program, has not been validated for Retinalamin using modern genomic and proteomic methods (e.g., chromatin immunoprecipitation sequencing, RNA sequencing, mass spectrometric identification of peptide-DNA complexes). The tissue-specificity claim, while consistent with cell culture observations, has not been tested against a comprehensive panel of non-retinal cell types in controlled comparative experiments. These limitations do not invalidate the clinical observations but do constrain the mechanistic interpretation and the ability to optimize the preparation rationally.

## 5. Pharmacokinetics

### 5.1 General considerations

Conventional pharmacokinetic analysis (absorption, distribution, metabolism, and elimination of a defined molecular entity) is not applicable to Retinalamin in the standard sense. The preparation consists of a mixture of polypeptide fractions of varying sequence and molecular weight, and the individual peptide components cannot be tracked independently in biological fluids using standard bioanalytical methods [4, 5]. The manufacturer's prescribing information states that the composition of Retinalamin does not permit the usual pharmacokinetic analysis of its components.

### 5.2 Routes of administration

Retinalamin is administered by two principal routes [4, 5]:

**Parabulbar injection.** The preparation is injected into the parabulbar space (the tissue surrounding the globe of the eye, posterior to the orbital septum), providing local delivery to the periocular tissues with presumed diffusion into the retinal and choroidal vasculature. This route achieves the highest local retinal concentrations and is the preferred route for focal retinal pathology.

**Intramuscular injection.** Systemic administration by intramuscular injection in the deltoid or gluteal region provides systemic distribution of the polypeptide fractions. Clinical studies have demonstrated that intramuscular administration produces retinoprotective effects comparable to parabulbar and retrobulbar administration, suggesting that the constituent peptides achieve functionally relevant retinal concentrations through systemic circulation [14].

### 5.3 Absorption and distribution

Following parabulbar injection, the polypeptide fractions are presumed to distribute locally through diffusion into periocular tissues and to reach the retina through choroidal and retinal vascular permeation. Following intramuscular injection, the peptides enter systemic circulation and distribute to retinal tissue through the

choroidal blood supply. The blood-retinal barrier presents a potential limitation to systemic delivery; however, the short peptide chain lengths (2 to 7 amino acids) and hydrophilic character of the principal fractions may facilitate transcellular passage.

## 5.4 Metabolism and elimination

Short peptides are generally metabolized rapidly by ubiquitous peptidases in plasma and tissues. The constituent peptides of Retinalamin are expected to be cleaved by aminopeptidases, carboxypeptidases, and endopeptidases to individual amino acids, which enter the general amino acid pool. The elimination half-life of individual peptide fractions has not been characterized. The clinical observation that therapeutic effects persist for months after a 5-to-10-day treatment course suggests that the biological activity is not dependent on sustained peptide concentrations but rather on downstream gene expression changes and cellular functional recovery that outlast the presence of the peptides themselves.

## 5.5 Comparative route efficacy

The Elichev et al. (2020) study of 498 patients with open-angle glaucoma compared three administration methods: combined intramuscular plus retrobulbar injection (5 mg each), retrobulbar injection alone (5 mg), and intramuscular injection alone (5 mg), with total treatment dose of 50 mg per patient [14]. All three routes produced comparable improvements in total threshold retinal sensitivity (122 to 274 decibels across glaucoma stages at 3 months), supporting the clinical equivalence of local and systemic administration and suggesting that the tissue-specific peptide activity is achieved regardless of the delivery route.

## 6. Preclinical Pharmacology

### 6.1 Morphogenetic activity in *Xenopus* ectodermal explants

Khavinson, Malinin, Trofimova, and Zemchikhina (2002) investigated the inductive activity of Retinalamin using early gastrula ectodermal explants from *Xenopus laevis* [7]. Ectodermal tissue, which in the absence of inductive signals differentiates into epidermis, was exposed to varying concentrations of Retinalamin. The results demonstrated that neuronal differentiation, including formation of brain, retinal, and pigment epithelium cell types, was dependent on Retinalamin concentration. At optimal concentrations, the preparation induced differentiation patterns characteristic of retinal and neural tissue. This study established the morphogenetic potency of the retinal peptide preparation and provided experimental support for the tissue-specificity hypothesis.

### 6.2 Retinal and pigmented epithelial cell proliferation

Khavinson, Zemchikhina, Trofimova, and Malinin (2003) examined the effects of Retinalamin and the synthetic tetrapeptide Epithalon on cultured retinal and pigmented epithelial cells from human and rat sources [8]. Both preparations stimulated cell proliferation in a tissue-specific manner: retinal cells and pigmented epithelial cells showed concentration-dependent increases in proliferative activity, while non-retinal cell types did not respond at the same concentrations. The tissue specificity of the proliferative response supported the interpretation that defined peptide sequences within the Retinalamin mixture interact with cell-type-specific regulatory elements.

### 6.3 Rabbit photochemical damage model

Suetov, Alekperov, Odinkaya, and Kostina (2021) evaluated the retinoprotective effects of Retinalamin in a rabbit model of photochemical retinal damage [13]. Thirty-six rabbits (72 eyes) were divided into four groups: two experimental groups receiving parabulbar Retinalamin injections at 0.25 mg/kg over 10 days (initiated on day 1 or day 10 of light exposure), and two control groups receiving saline. All animals

were exposed to 405-nanometer light at 5 mW/cm<sup>2</sup> for 4 hours daily over 20 days. Endpoints included multifocal and 30-Hz flicker electroretinography and histological examination with TUNEL apoptosis quantification, assessed at days 10, 20, and 30. Ophthalmoscopic signs of light-induced retinal degeneration appeared in all groups between days 6 and 10. No significant functional or morphological evidence of neuroprotective effects of Retinalamin was found, with amplitude decreases in N1 and P1 peaks occurring similarly across treated and control groups. This negative preclinical finding is notable and contrasts with the positive clinical observations; it may reflect model-specific factors, dosing adequacy, or the difficulty of translating clinical peptide bioregulator effects to acute photodamage paradigms.

# 7. Clinical Evidence Base

## 7.1 Open-angle glaucoma

The largest body of controlled clinical evidence for Retinalamin is in compensated primary open-angle glaucoma, where the compound is positioned as an adjunctive neuroprotective therapy for patients with controlled intraocular pressure.

**Egorov et al. (2019) randomized controlled trial.** This study enrolled 180 patients (355 eyes) with primary open-angle glaucoma and compensated intraocular pressure, randomized to intramuscular Retinalamin (main group, n=90) or no neuroprotective treatment (control group, n=90) [9]. The treatment group received intramuscular Retinalamin injections according to standard protocol. Key results: visual field mean deviation index improved from negative 5.52 plus or minus 2.76 to negative 4.82 plus or minus 2.73 decibels in treated patients, while control patients showed deterioration. Ganglion cell complex thickness remained stable in the treatment group but thinned progressively in controls. Pattern electroretinography P50 and N95 amplitudes remained stable with Retinalamin. Intraocular pressure showed no significant changes in either group. The investigators concluded that systemic use of Retinalamin has significant retinoprotective effect confirmed by dynamics of morphological and functional parameters.

**Strakhov et al. (2020) randomized controlled trial.** This 24-month study enrolled 147 patients (249 eyes) with stage I to II primary open-angle glaucoma [10]. The treatment group (69 patients, 119 eyes) received Retinalamin courses every 6 months; the control group (78 patients, 130 eyes) received no neuroprotective treatment. Results demonstrated that retinal nerve fiber layer thickness remained stable in the treatment cohort versus declining from 83.5 to 76.7 micrometers in controls. Neuroretinal rim area increased in the treatment group (222 to 231 arbitrary units) versus decreased in controls. The investigators concluded that regular treatment with Retinalamin arrests the development of glaucomatous optic neuropathy.

**Erichev et al. (2020) comparative route study.** This 498-patient study compared three Retinalamin administration methods in open-angle glaucoma (initial, moderate, and advanced stages): combined intramuscular plus retrobulbar (Group I, n=110), retrobulbar only (Group II, n=171), and intramuscular only (Group III) [14].

Total treatment dose was 50 mg per patient. At 3 months, total threshold retinal sensitivity increased by 122 decibels in patients with initial glaucoma (Group I), with comparable improvements across groups. The investigators determined that intramuscular, retrobulbar, and combined administration methods have comparable efficacy, with best outcomes in initial and moderate glaucoma stages.

**Makashova et al. (2014) case report.** A single case report described application of Retinalamin (10 parabulbar injections) in a patient with newly diagnosed glaucoma and therapeutically normalized intraocular pressure, with functional assessments by Humphrey perimetry, Heidelberg retina tomography, and electrophysiology at baseline, 1 month, and 3 months post-treatment [15].

## 7.2 Diabetic retinopathy

**Malakhova et al. (2024) comparative study.** This study enrolled 56 patients (112 eyes) with type 1 and type 2 diabetes and diabetic retinopathy without macular edema [16]. The treatment group (28 patients, 56 eyes) received intramuscular Retinalamin; the control group (28 patients, 56 eyes) received no Retinalamin. Objective monitoring by optical coherence tomography and electrophysiological testing (Diopsys Nova system) demonstrated convincing objective evidence of positive changes in the treatment group. The findings support neuroprotective potential of Retinalamin during early diabetic retinopathy stages.

## 7.3 Retinal dystrophies and abiotrophy

**Razumovskiy et al. long-term outcomes study.** This observational study evaluated three groups: Group I (20 patients, 40 eyes) treated with Retinalamin for 5 to 7 years; Group II (11 patients, 22 eyes) treated for 23 to 25 years; and Group III (15 patients, 30 eyes) receiving traditional therapy without Retinalamin for 25 years [12]. All patients had pigmentary retinal dystrophy or retinal abiotrophy. The first course of Retinalamin improved vision in 58.1 percent and visual fields in 64.5 percent of retinal degeneration patients. Total area of absolute scotomas decreased after initial treatment. With repeated courses (1 to 2 times per year over 23 to 25 years), residual vision was preserved in 55.6 percent of patients and object vision was preserved in 11.1 percent of cases. In retinal abiotrophy patients, residual vision was preserved in 100 percent of cases. The investigators concluded that

Retinalamin improves vision and visual fields and decreases total area of absolute scotomas even after the first treatment course and preserves vision in prolonged use.

## 7.4 Ocular tuberculosis

Retinalamin has been studied as a bioregulatory adjunctive treatment in patients with tuberculosis of the organ of vision, specifically tuberculous chorioretinitis [17]. The evidence in this indication is limited to case series and exploratory reports; no controlled trials have been published.

## 7.5 Myopic disease

Retinalamin is indicated in the Russian registration for myopic disease as part of comprehensive treatment, administered by parabulbar injection at 5 mg daily for 10 days [4]. Clinical evidence for this indication is limited and has not been characterized in controlled trials in the peer-reviewed literature.

## 7.6 Quality of life outcomes

A 2006 study evaluated the effect of bioregulating therapy including Retinalamin on the quality of life of elderly patients with retinal pathology, reporting improvements in subjective visual function and quality-of-life measures [18].

## 7.7 Limitations of the clinical evidence base

The clinical evidence for Retinalamin is subject to several important limitations. The majority of published studies originate from a concentrated group of Russian ophthalmological centers. Published trials have not uniformly employed double-masking, sham-injection controls, or intention-to-treat analysis. Sample sizes are modest by international registration standards. The primary literature is predominantly in Russian, limiting independent critical review. No study has been registered prospectively in ClinicalTrials.gov or an equivalent international trial registry. These limitations do not invalidate the reported findings but necessitate cautious interpretation and underscore the need for independent replication in methodologically rigorous, internationally supervised trials.

## 8. Sourcing and Quality Verification

### 8.1 Pharmaceutical-grade sources

The pharmaceutical-grade preparation is manufactured exclusively by Geropharm LLC (Russian Federation) in partnership with the St. Petersburg Institute of Bioregulation and Gerontology [4]. The branded Retinalamin product is supplied as a lyophilisate for reconstitution in 5-milligram glass vials, 10 vials per package. The pharmaceutical-grade material is available through Russian pharmacies and through international exporters specializing in Russian pharmaceutical products.

### 8.2 Research-grade and supplement sources

Retinalamin is available from multiple online vendors marketing Russian pharmaceutical products internationally, including CosmicNootropic, RuPharma, RxEli, and others. These vendors typically supply the Geropharm-manufactured pharmaceutical product rather than independently synthesized material. The compound is also available from peptide bioregulator specialty vendors that supply the broader Khavinson peptide product line.

### 8.3 Quality verification considerations

Because Retinalamin is a multi-component biological extract rather than a single chemical entity, analytical verification is more complex than for defined small molecules. Investigators should confirm:

- Supplier documentation of manufacture by Geropharm LLC under current Russian Good Manufacturing Practice standards
- Batch-specific certificate of analysis including peptide content, amino acid composition profile, sterility testing, and bacterial endotoxin testing
- Product packaging integrity, including intact seals on lyophilisate vials
- Storage conditions during transport (2 to 25 degrees Celsius)
- Expiration dating on packaging

Independent analytical verification by third-party laboratories is limited by the absence of a defined reference standard for the polypeptide mixture. HPLC peptide profiling and amino acid analysis can confirm the general character of the preparation but cannot verify identity against a pharmacopoeial monograph, as no such monograph exists outside the Russian Federation.

## 8.4 Counterfeit and substitution risk

The multi-component nature of Retinalamin and the absence of a single-entity analytical reference standard create a higher counterfeit risk than for defined chemical compounds. Investigators should source from documented Geropharm supply chains and should confirm product authenticity through packaging verification, batch traceability, and (where feasible) amino acid composition analysis.

## 9. Reconstitution and Handling

### 9.1 Reconstitution protocol

Retinalamin lyophilisate is reconstituted immediately before use [4, 5]. The contents of one vial (5 mg Retinalamin plus 17 mg glycine) are dissolved in 1 to 2 milliliters of one of the following diluents:

- Water for injection (sterile, pyrogen-free)
- 0.9 percent sodium chloride solution for injection
- 0.5 percent procaine (novocaine) solution for injection

The diluent is directed toward the wall of the vial (not directly onto the lyophilized cake) to avoid foaming. The vial is gently swirled until complete dissolution is achieved. The reconstituted solution should be clear and free of visible particulate matter.

### 9.2 Administration

**Parabulbar injection:** The reconstituted solution (0.5 to 1.0 mL containing 5 mg Retinalamin) is injected into the parabulbar space under aseptic conditions. Injection is performed with a fine-gauge needle (typically 25 to 27 gauge) through the lower eyelid, directed posteriorly along the orbital floor.

**Intramuscular injection:** The reconstituted solution (1 to 2 mL containing 5 to 10 mg Retinalamin) is injected into the deltoid or gluteal muscle under standard intramuscular injection technique.

### 9.3 Incompatibilities

Retinalamin should not be mixed with other medicinal products in the same syringe [4, 5]. No specific chemical incompatibilities have been characterized, but the multi-component nature of the preparation creates unpredictable interaction potential with other injectable formulations.

## 9.4 Storage

The lyophilized product is stored at 2 to 25 degrees Celsius in the original packaging, protected from light, and kept out of reach of children [4]. The reconstituted solution should be used immediately and should not be stored. Unused reconstituted solution should be discarded.

# 10. Stack Interactions and Combinations

## 10.1 Drug interactions

No specific drug-drug interactions have been characterized for Retinalamin in formal pharmacokinetic interaction studies [4, 5]. The multi-component polypeptide nature of the preparation and the absence of conventional pharmacokinetic data preclude standard interaction prediction based on cytochrome P450 enzyme inhibition or induction, transporter substrate status, or plasma protein binding displacement.

## 10.2 Concomitant ophthalmic therapy

Retinalamin is used clinically as an adjunctive therapy alongside standard treatments for its indicated conditions. Concurrent use with the following drug classes is common in the published clinical literature:

**Intraocular pressure-lowering agents.** In glaucoma patients, Retinalamin is administered concurrently with topical prostaglandin analogs (latanoprost, travoprost, bimatoprost), beta-adrenergic antagonists (timolol), carbonic anhydrase inhibitors (dorzolamide, brinzolamide), and alpha-2 adrenergic agonists (brimonidine) without reported adverse interactions [9, 10, 11].

**Anti-VEGF agents.** In diabetic retinopathy, concurrent use with intravitreal anti-VEGF agents (ranibizumab, aflibercept, bevacizumab) has not been specifically studied, though temporal separation of injections is prudent given the separate injection sites and the potential for additive ocular inflammation.

**Systemic antidiabetic therapy.** In diabetic retinopathy patients, Retinalamin is administered alongside systemic glycemic control agents (insulin, metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists) without reported interactions [16].

## 10.3 Combinations with other peptide bioregulators

In the Khavinson peptide bioregulator paradigm, combinations of tissue-specific peptide preparations are sometimes employed for systemic therapeutic effect. Retinalamin has been combined with Cortexin (brain-derived peptides) for conditions involving both retinal and central nervous system pathology. The pharmacological rationale is that tissue-specific peptides act independently on their target tissues without pharmacokinetic interference. No formal interaction studies have characterized these combinations.

## 10.4 Considerations for research stack design

Investigators incorporating Retinalamin into multi-compound research protocols should consider: the absence of conventional pharmacokinetic data, which prevents prediction of exposure changes in combination; the immunogenic potential of repeated bovine-derived polypeptide administration, which may be potentiated by concurrent immunomodulatory agents; and the absence of defined receptor targets, which prevents rational prediction of pharmacodynamic interactions at the receptor level.

# 11. Adverse Events and Safety

## 11.1 Common adverse events

The adverse event profile of Retinalamin is favorable, with the principal reported events being local injection-site reactions [4, 5]:

- Pain at the injection site (parabulbar or intramuscular; frequency not quantified in published literature but reported as common)
- Redness at the injection site
- Swelling at the injection site

These local reactions are self-limiting and are managed with standard post-injection care. No dose-dependent increase in injection site reactions has been characterized.

## 11.2 Rare and serious adverse events

Rare serious adverse events reported in the prescribing information include [4]:

- Anaphylactic shock (frequency not quantified; reported as a class risk for biological preparations)
- Angioneurotic laryngeal edema (frequency not quantified)

These events are consistent with hypersensitivity to bovine-derived polypeptide material and are a theoretical risk with any biological product of animal origin. No fatal adverse events have been reported in the published literature.

## 11.3 Temporary visual disturbance

The prescribing information notes that temporary visual disturbances may occur following parabulbar injection [4]. This is consistent with the mechanical effects of periocular injection (temporary blurring from tissue swelling and local anesthetic effects when procaine is used as diluent) rather than with direct pharmacological toxicity. Patients are advised to exercise caution when driving or operating machinery after parabulbar injection.

## 11.4 Contraindications

Retinalamin is contraindicated in the following populations [4, 5]:

- Individuals with known hypersensitivity to any component of the preparation (including glycine excipient or bovine-derived polypeptide material)
- Pregnant women (contraindicated due to absence of clinical safety data)
- Breastfeeding women (nursing should be discontinued if Retinalamin treatment is necessary)
- Patients under 18 years of age for compensated primary open-angle glaucoma, diabetic retinopathy, myopia, and post-surgical retinal detachment rehabilitation (insufficient efficacy and safety data)
- Patients under 12 months of age for post-traumatic and post-inflammatory central retinal dystrophy and tapetoretinal abiotrophy

## 11.5 Overdose

No cases of overdose have been reported. Given the peptide nature of the compound and the rapid degradation of short peptides by endogenous peptidases, acute toxicity from single-dose overdose is considered unlikely [4].

## 11.6 Long-term safety

Long-term safety data are available from observational studies of patients receiving biannual Retinalamin courses over periods of up to 25 years [12]. No cumulative toxicity, immunogenicity-related adverse events, or organ system damage has been reported in these long-term observations. The absence of systematic long-term safety monitoring (e.g., immunoglobulin titers against bovine peptides, hepatic and renal function panels, hematological monitoring) in the published literature limits the strength of these safety observations.

## 11.7 Immunogenicity considerations

As a bovine-derived polypeptide preparation, Retinalamin carries a theoretical risk of immunogenic responses including anti-peptide antibody formation, delayed-type hypersensitivity, and cross-reactive autoimmune phenomena. No formal immunogenicity studies have been published. The low molecular weight of the constituent peptides (predominantly below 1,000 daltons) reduces but does not elimi-

nate immunogenic potential. Investigators using Retinalamin in research settings should consider monitoring for anti-bovine-peptide antibodies in subjects receiving repeated treatment courses.

## 12. Comparative Assessment

This section presents a structured comparative assessment of five alternative retinal neuroprotective agents against Retinalamin, evaluated on five standards: novelty, effect size, clinical development status, side-effect profile, and overall validation. The comparators were selected to span the principal pharmacological approaches to retinal neuroprotection: neurotrophic factors, alpha-2 adrenergic agonists, antioxidants, and alternative peptide preparations.

### 12.1 Brimonidine (alpha-2 adrenergic agonist)

**Mechanism:** Highly selective alpha-2 adrenergic receptor agonist. Reduces intraocular pressure through reduction of aqueous humor production and stimulation of uveoscleral outflow. Independently neuroprotective through upregulation of brain-derived neurotrophic factor (BDNF) expression in retinal ganglion cells, modulation of NMDA receptor-mediated excitotoxicity, and anti-apoptotic signaling through Akt phosphorylation [19, 20].

**Novelty:** Moderate. The alpha-2 agonist neuroprotective mechanism is well characterized and represents a distinct approach from peptide bioregulation. The dual IOP-lowering and neuroprotective mechanism is clinically established.

**Effect size:** In the Low-Pressure Glaucoma Treatment Study, brimonidine monotherapy showed significantly lower visual field progression (9.1 percent) compared to timolol (39.2 percent) despite similar IOP reduction, suggesting IOP-independent neuroprotective benefit [21]. Effect sizes in neuroprotection-specific outcomes are clinically meaningful.

**Clinical development status:** Brimonidine is FDA-approved and globally registered for glaucoma and ocular hypertension. The neuroprotective indication is supported by clinical evidence but is not a separately approved indication. The compound has a robust international regulatory and clinical evidence base.

**Side-effect profile:** Ocular allergy (conjunctival hyperemia, pruritus) in approximately 10 to 15 percent of patients with chronic topical use. Systemic side effects include dry mouth, fatigue, and drowsiness. The side-effect profile is well characterized through decades of clinical use.

**Overall validation:** High. Brimonidine is the most clinically validated retinal neuroprotective agent with independent, IOP-independent neuroprotective activity demonstrated in a randomized controlled trial.

**Comparison to Retinalamin:** Brimonidine has a defined molecular target, a comprehensive pharmacokinetic profile, international regulatory approval, and large-scale clinical trial evidence. Retinalamin has a fundamentally different mechanism (multi-peptide gene regulation versus single-target receptor agonism) and a geographically concentrated evidence base. For retinal neuroprotection research, brimonidine serves as the reference standard against which novel agents including Retinalamin should be compared.

## 12.2 Ciliary Neurotrophic Factor (CNTF, NT-501 device)

**Mechanism:** CNTF is a hypothalamic neuropeptide and neuronal survival factor that activates the JAK-STAT signaling pathway through the CNTF receptor alpha, gp130, and LIF receptor beta complex. CNTF promotes retinal ganglion cell survival, protects photoreceptors in multiple models of retinal degeneration, and enhances glycolysis and anabolism in degenerating retinas [22, 23].

**Novelty:** Moderate to high. The sustained intraocular delivery via encapsulated cell technology (NT-501 implant by Neurotech Pharmaceuticals) represents a novel delivery platform for retinal neuroprotection.

**Effect size:** CNTF delivered by NT-501 has demonstrated photoreceptor preservation in retinitis pigmentosa, geographic atrophy, and macular telangiectasia Type 2 in Phase 2 clinical trials. Effect sizes on structural endpoints (outer nuclear layer thickness) have been significant; functional endpoints (visual acuity) have shown variable results [23].

**Clinical development status:** Phase 2 trials completed for multiple retinal indications. Phase 3 trial underway for macular telangiectasia Type 2. Not yet FDA-approved for any retinal indication.

**Side-effect profile:** The NT-501 implant requires surgical insertion and removal. Device-related adverse events include transient anterior chamber inflammation, device migration, and procedural complications. CNTF-specific adverse effects are minimal owing to the contained delivery system.

**Overall validation:** Moderate. Substantial preclinical support and Phase 2 clinical evidence, with pending Phase 3 outcomes. The delivery technology is the principal innovation.

**Comparison to Retinalamin:** CNTF represents a single-factor neurotrophic approach, while Retinalamin is a multi-peptide bioregulator. CNTF has a more advanced international clinical development trajectory but requires an implantable device; Retinalamin is administered by simple injection courses. The two approaches are mechanistically distinct and potentially complementary.

## 12.3 Cortexin (brain-derived peptide bioregulator)

**Mechanism:** Cortexin is a polypeptide preparation derived from bovine brain cortex, belonging to the same Khavinson peptide bioregulator class as Retinalamin. It consists of water-soluble polypeptide fractions with molecular weight below 10,000 daltons and acts through gene expression modulation in neuronal tissue [1, 2]. Cortexin has been used in ophthalmological practice for conditions involving both retinal and central visual pathway pathology.

**Novelty:** Low (within the peptide bioregulator class). The mechanism and pharmacological paradigm are essentially identical to Retinalamin, differing only in tissue source (brain cortex versus retina) and therefore in the specific peptide composition.

**Effect size:** Clinical evidence for Cortexin in retinal indications is sparse. The compound is primarily positioned for neurological rather than ophthalmological applications. Reported effects on retinal function are modest and insufficiently characterized in controlled studies.

**Clinical development status:** Registered in the Russian Federation for neurological indications. Not registered for ophthalmological indications. Not approved internationally.

**Side-effect profile:** Similar to Retinalamin: local injection site reactions and rare hypersensitivity. The bovine-derived biological preparation carries the same theoretical immunogenicity risk.

**Overall validation:** Low for retinal indications. The compound serves as a within-class comparator for Retinalamin but does not represent an alternative for retinal neuroprotection with independent supporting evidence.

**Comparison to Retinalamin:** Retinalamin is tissue-specifically derived from retinal tissue and has a substantially larger ophthalmological clinical evidence base than Cortexin. The tissue-specificity paradigm predicts that Retinalamin should be more active on retinal cells than the brain-derived Cortexin, and this prediction is consistent with the clinical use patterns.

## 12.4 Citicoline (cytidine-5'-diphosphocholine)

**Mechanism:** Citicoline is an endogenous nucleotide involved in the synthesis of phosphatidylcholine, a major component of neuronal cell membranes. It provides neuroprotection through membrane stabilization, reduction of phospholipase A2 activity, maintenance of sphingomyelin and cardiolipin levels, enhancement of dopamine synthesis, and anti-apoptotic effects. In the retina, citicoline has been shown to protect retinal ganglion cells and to improve visual function in glaucoma and amblyopia [24].

**Novelty:** Low. Citicoline has been studied for neurological and ophthalmological applications for decades. The mechanism is well established.

**Effect size:** Multiple randomized controlled trials have demonstrated retinal ganglion cell protection and visual field improvement in glaucoma patients treated with oral or intramuscular citicoline. The CITRY study (2022) demonstrated significant visual field improvement with topical citicoline eye drops in glaucoma patients [24]. Effect sizes are modest but reproducible.

**Clinical development status:** Available as a dietary supplement in many jurisdictions. Registered as a pharmaceutical in some European and Asian countries. Topical ophthalmic formulations are in clinical development. Not FDA-approved for ophthalmological indications.

**Side-effect profile:** Excellent. Citicoline has a well-established safety profile with minimal adverse events. Gastrointestinal symptoms are the principal reported side effects at oral doses.

**Overall validation:** Moderate to high. Citicoline has a broader international evidence base for retinal neuroprotection than Retinalamin, with multiple independent research groups contributing controlled trial data.

**Comparison to Retinalamin:** Citicoline offers a defined single-molecule neuro-protective approach with international evidence, while Retinalamin offers a tissue-specific multi-peptide approach with geographically concentrated evidence. Citicoline has superior ease of administration (oral, topical) compared to Retinalamin (injection only). Both compounds share the positioning of adjunctive neuroprotection in glaucoma with modest effect sizes.

## 12.5 Recombinant BDNF (Brain-Derived Neurotrophic Factor)

**Mechanism:** BDNF is a neurotrophin that signals through the TrkB receptor tyrosine kinase to promote neuronal survival, axonal growth, and synaptic plasticity. In the retina, BDNF supports retinal ganglion cell survival and photoreceptor maintenance through activation of the PI3K/Akt and MAPK/ERK signaling cascades [25].

**Novelty:** Low. BDNF has been studied as a retinal neuroprotective agent for over two decades. The principal innovation is in delivery technology rather than in the molecule itself.

**Effect size:** Preclinical evidence demonstrates substantial retinal ganglion cell protection with intravitreal BDNF. Clinical evidence is limited owing to the short half-life of the protein in the vitreous and the requirement for repeated intravitreal injections or sustained-release devices.

**Clinical development status:** No approved product. Clinical translation has been hampered by the pharmacokinetic limitations of protein delivery to the retina. Sustained-release formulations and gene therapy approaches for BDNF delivery are in preclinical and early clinical development.

**Side-effect profile:** Intravitreal injection-related adverse events (endophthalmitis risk, retinal detachment, vitreous hemorrhage) are the principal concerns. BDNF-specific toxicity has not been identified at therapeutic doses.

**Overall validation:** Low to moderate as a standalone therapeutic. High as a mechanistic reference standard for retinal neuroprotection research.

**Comparison to Retinalamin:** BDNF represents a single-factor neurotrophic approach with robust preclinical support but limited clinical translation, while Retinalamin has an established clinical use pattern despite weaker mechanistic

characterization. The two approaches are conceptually related (both aim to support retinal neuron survival) but differ fundamentally in molecular definition and regulatory status.

## 12.6 Comparator summary

The five comparators span the retinal neuroprotection landscape from defined single-molecule agents (brimonidine, citicoline, BDNF) through novel delivery platforms (CNTF/NT-501) to within-class peptide bioregulators (Cortexin). **Brimonidine** is the most clinically validated retinal neuroprotective agent with independent trial evidence of IOP-independent neuroprotection and international regulatory approval. CNTF represents an innovative delivery approach with Phase 2/3 evidence. **Citicoline** offers a well-tolerated, widely available neuroprotective agent with growing controlled trial evidence. **Cortexin** serves as a within-class comparator that highlights Retinalamin's tissue-specific advantage within the peptide bioregulator paradigm. **BDNF** is the mechanistic reference standard with limited clinical translation.

Retinalamin occupies a distinctive position in this landscape as the only tissue-specific retinal peptide bioregulator with a multi-decade clinical use history. Its principal advantages are tissue specificity, favorable safety profile, established clinical protocols, and the multi-target nature of the polypeptide mixture (which may engage multiple protective mechanisms simultaneously). Its principal disadvantages are the absence of international regulatory approval, the geographically concentrated evidence base, the undefined molecular composition, the absence of conventional pharmacokinetic data, and the negative finding in the Suetov et al. (2021) rabbit photodamage model. The compound's positioning is therefore best understood as an adjunctive neuroprotective therapy with substantial clinical experience in Russian ophthalmological practice, requiring independent international validation to establish its place in the broader retinal neuroprotection armamentarium.

## 13. References

1. Khavinson VK. Peptides and Ageing. *Neuroendocrinol Lett.* 2002;23(Suppl 3):11-144.
2. Khavinson VK, Kuznik BI, Ryzhak GA. Peptide bioregulators: a new class of geroprotectors. Message 1: Results of experimental studies. *Adv Gerontol.* 2013;3(3):225-235.
3. Khavinson VK, Trofimova SV. Retinalamin. In: *Peptide Bioregulators in Ophthalmology*. St. Petersburg: Foliant; 2004.
4. Retinalamin prescribing information. Geropharm LLC, Russian Federation. ATC Code S01XA.
5. Retinalamin product monograph. Geropharm LLC. Available at: [cosmicnootropic.com/instructions/retinalamin-instruction/](http://cosmicnootropic.com/instructions/retinalamin-instruction/).
6. Khavinson VK, Zemchikhina VN, Trofimova SV, Malinin VV. Effects of peptides on proliferative activity of retinal and pigmented epithelial cells. *Bull Exp Biol Med.* 2003;135(6):597-599.
7. Khavinson VK, Malinin VV, Trofimova SV, Zemchikhina VN. Inductive activity of retinal peptides. *Bull Exp Biol Med.* 2002;134(5):482-484.
8. Khavinson VK, Zemchikhina VN, Trofimova SV, Malinin VV. Effects of peptides on proliferative activity of retinal and pigmented epithelial cells. *Bull Exp Biol Med.* 2003;135(6):597-599.
9. Egorov EA, Elichev VP, Strakhov VV, et al. Structural and functional changes in the retina of patients with primary open-angle glaucoma and compensated intraocular pressure while undergoing retinoprotective therapy. *Vestn Oftalmol.* 2019;135(3):20-30.
10. Strakhov VV, Egorov EA, Elichev VP, et al. The influence of long-term retinal protective therapy on glaucoma progression according to structural and functional tests. *Vestn Oftalmol.* 2020;136(5):58-66.

11. Makashova NV, Vasil'eva AE, Morozova NE, Ronzina IA. Application of Retinalamin for the treatment of glaucomatous optic neuropathy. *Vestn Oftalmol.* 2014;130(4):68-71.
12. Razumovskiy MI, et al. Long-term outcomes of retinal degenerative disorder treatment with peptide bioregulators. *Ophthalmology in Russia (Oftal'mologiya)*. Published online.
13. Suetov AA, Alekperov SI, Odinokaya MA, Kostina AA. Retinoprotective effects of Retinalamin studied in an experimental model of photochemical damage to rabbit retinas. *Vestn Oftalmol.* 2021;137(5):57-67.
14. Erichev VP, Lovpache DN, Yaremenko TV. Peptide bioregulators: delivery and efficacy. *Vestn Oftalmol.* 2020;136(2):56-62.
15. Makashova NV, Vasil'eva AE, Morozova NE, Ronzina IA. Application of Retinalamin for the treatment of glaucomatous optic neuropathy. *Vestn Oftalmol.* 2014;130(4):68-71.
16. Malakhova AI, Strakhov VV, Malakhova YA. Objective structural and functional monitoring of polypeptide retinal neuroprotective therapy in diabetic retinopathy. *Vestn Oftalmol.* 2024;140(5):97-104.
17. Treatment with the peptide bioregulator retinalamine in patients with tuberculosis of the organ of vision. *Probl Tuberk Bolezn Legk.* 2008;(2):40-43.
18. The effect of the bioregulating therapy on the quality of life of elderly patients with retinal pathology. *Adv Gerontol.* 2006;19:76-81.
19. Dong CJ, Guo Y, Agey P, Wheeler L, Hare WA. Alpha-2 adrenergic modulation of NMDA receptor function as a major mechanism of RGC protection in experimental glaucoma and retinal excitotoxicity. *Invest Ophthalmol Vis Sci.* 2008;49(10):4515-4522.
20. Lai RK, Chun T, Hasson D, Lee S, Mehrbod F, Wheeler L. Alpha-2 adrenoceptor agonist protects retinal function after acute retinal ischemic injury in the rat. *Vis Neurosci.* 2002;19(2):175-185.
21. Krupin T, Liebmann JM, Greenfield DS, et al. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *Am J Ophthalmol.* 2011;151(4):671-681.

22. Pease ME, Zack DJ, Bhatt N, et al. Effect of CNTF on retinal ganglion cell survival in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2009;50(5):2194-2200.
  23. Wang SK, Xue Y, Cepko CL. Ciliary neurotrophic factor-mediated neuroprotection involves enhanced glycolysis and anabolism in degenerating mouse retinas. *Nat Commun*. 2022;13(1):7037.
  24. Parisi V, Centofanti M, Ziccardi L, et al. Treatment with citicoline eye drops enhances retinal function and neural conduction along the visual pathways in open angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(8):1327-1340.
  25. Mansour-Robaey S, Clarke DB, Wang YC, Bhatt GG, Bhatt N. Effects of ocular injury and administration of brain-derived neurotrophic factor on survival and regrowth of axotomized retinal ganglion cells. *Proc Natl Acad Sci USA*. 1994;91(5):1632-1636.
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