(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 September 2009 (24.09.2009)

PCT

(10) International Publication Number
WO 2009/116076 A2

(51) International Patent Classification:
A61K 9/08 (2006.01) *A61K 31/44* (2006.01)

(21) International Application Number:
PCT/IN2009/000113

(22) International Filing Date:
19 February 2009 (19.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
355/MUM/2008 19 February 2008 (19.02.2008) IN

(71) Applicant *(for all designated States except US)*: **M. J. BIOPHARM PVT.LTD.** [IN/IN]; 113, Jolly Maker Chambers No. 2, Nariman Point, Mumbai-400 021, Maharashtra (IN).

(72) Inventors: **VYAS, Ashok, Vasantray**; 26-27, Shakti Nagar Society, Gotri Road, Vadodara-390 021, Gujarat (IN). **JADHAV, Ravindra, Tukaram**; 304, Susheel Residency, Plot No. 67/1, Panvel-410 206, Maharashtra (IN). **PHAD, Subhash, Trimbak**; 202, Creative Arcade, Vijay Nagar Colony, Kukatpally, Hyderabad-500 072, Andhra Pradesh (IN).

(74) Agent: **MOHAN Dewan**; K. DEWAN & COMPANY, Podar Chambers, S.A. Brelvi Road, Fort, Mumbai 400 001, Maharashtra (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2009/116076 A2

(54) Title: STERILE OPTHALMIC PREPARATIONS AND A PROCESS FOR PREPARATION THEREOF

(57) Abstract: An ophthalmic composition comprising 3-hydroxy 2,4,6 trimethylpyridine, pharmaceutically acceptable salts, esters, derivatives and polymorphs thereof for the treatment of intraocular hemorrhage and macular degeneration is disclosed.

STERILE OPTHALMIC PREPARATIONS AND A PROCESS FOR PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to an ophthalmic composition.

Particularly, the present invention relates to an ophthalmic composition used in the treatment of intraocular hemorrhage and macular degeneration.

BACKGROUND OF THE INVENTION

Intraocular hemorrhage (hemophthalmos or hemophthalmia) is a condition in which bleeding occurs in the eyeball . It may be the result of physical trauma (direct injury to the eye) and/or medical illness. Severe hemorrhage, particularly when leading to rising pressure inside the eye, may lead to blindness.

There are different types of intraocular hemorrhage such as subconjunctival hemorrhage, hyphema, vitreous hemorrhage ,subretinal hemorrhage and submacular hemorrhage. Different causes responsible for bleeding in different locations are terson's syndrome (as a result of subarachnoid hemorrhage), hemophilia (a severe bleeding disorder, usually hereditary) , anticoagulants and thrombolysis (medication to reduce blood clotting tendency or to disperse blood clots, respectively)

It has been proved that hemophthalmia is always accompanied by activation of free radical oxidation processes and proceeded as chain reactions and involves accumulation of oxidation products of molecules in vitreous body and retina. Application of antioxidant preparations in early conservative therapy of intraocular hemorrhages essentially allows to speed up the resorption processes and thus reduce the risk of development of serious complications such as fibrosis of vitreous body and retinal detachment.

In the last decade researches of have established that inflammatory reaction is always accompanied by activation of processes of free radical oxidation, mutually

aggravating each other and resulting in development of various post-inflammatory complications. Use of antioxidant in early conservative therapy of inflammatory pathology of eye allows to speed up the recovery and to improve the disease prognosis.

3-Hydroxy-2,4,6-trimethylpyridine succinate and other such salts belong to new biologically active compounds which exhibit important pharmacological activities such as anti oxidant for the vascular and inflammatory eye pathology. 3-Hydroxy-2,4,6-trimethylpyridine succinate and other such salts also possess geroprotective action and can be used to treat conditions, diseases or disorders of the cornea, retina, lens, sclera , anterior and posterior segments of the eye.

Another critical indication where the aforementioned compound finds its use is macular degeneration (degenerative disease of the eye). In macular degeneration, lipofuscin accumulation is implicated as a major risk factor. Lipofuscin is finely granular yellow brown pigment, composed of lipid-containing residues of lysosomal digestion. It is considered one of the aging or "wear and tear" pigments. It appears to be the product of the oxidation of unsaturated fatty acids and may be symptomatic of membrane damage or damage to mitochondria and lysosomes.

3-Hydroxy-2,4,6-trimethylpyridine has been found to be an active inhibitor of peroxide oxidation of lipids. Thus, it is capable of neutralizing toxic activity of lipofuscin granules to have geroprotective action.

EXISTING KNOWLEDGE

PCT/IB2005/003636 discloses a method of preparing 2,4,6-trimethyl-3-hydroxypyridine derivatives and salts thereof having antioxidant, geroprotective and anti-ischemic activity.

This patent application suggest the use of 2,4,6-trimethyl-3-hydroxypyridine derivatives as a geroprotective and anti ischemic. Disclosure of the said Pct application is limited to a method of synthesis of 2, 4, 6-trimethyl-3-

hydroxypyridine derivative and salts. However, details of the formulations comprising said 2,4,6-trimethyl-3-hydroxypyridine derivative or salts have not been disclosed.

Accordingly, it is desirable to prepare a pharmaceutically acceptable dosage form containing 2, 4, 6-trimethyl-3-hydroxypiridine for the treatment of various eye diseases.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide to provide a geroprotective and antioxidant formulation.

It is another object of the present invention to provide an ophthalmic formulation for therapeutic and/or prophylactic purpose in various eye diseases.

It is yet another objective of the present invention to provide a stable pharmaceutically acceptable ophthalmic formulation.

It is a further object of this invention to provide an ophthalmic formulation which does not cause irritation at the site of application.

It is still further object of the present invention to provide an ophthalmic formulation that provides patient compliance.

It is another object of the present invention to provide an ophthalmic formulation which is easy to prepare and is cost effective.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided an ophthalmic composition comprising 3-hydroxy- 2,4,6-trimethylpyridine, pharmaceutically acceptable salts, esters, derivatives and polymorphs thereof in an amount in the range of about 0.05 % to about 10 % of the mass of the composition, preservative in the range of about 0.005 % to about 0.5% of the mass of the composition,

stabilizer in the range of about 0.01 % to about 1% of the mass of the composition, excipients in the range of about 0.02 % to about 5 % of the mass of the composition and a vehicle, wherein pH of said ophthalmic composition is in the range of about 4 to about 7.5.

Typically, the pharmaceutically acceptable salt of 3-hydroxy-2,4,6-trimethylpyridine is selected from a group of salts consisting of succinate, maleate, tartarate, oxalate, fumarate, citrate , hydrochloride, salicylate, pamoate, hydrogen sulfate, sulfate, methanesulphonate and benzenesulfonate.

Typically, the preservative is at least one selected from a group consisting of benzalkonium chloride, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, chlorobutanol, metacresol, phenylmercuric nitrate, phenylmercuric acetate orphenylmercuric borate, thiomersal, myristylgamma picolonium chloride, phenol, benzoxonium chloride, cetrimide, phenyl ethanol, chlorohexidine and sodium perborate.

Typically, the stabilizer is selected from a group consisting of thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol, sodium edetate, creatinine, glycine, niacinamide, sodium acetyltryptophanate, sodium caprylate, sodium saccharin, citric acid and salts thereof.

Typically, the excipients are selected from a group consisting of thickening agents, chelating agents, buffering agent, surfactants, tonicity agents, pH adjusting agents and solvents.

Typically, the thickening agent is at least one selected from a group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose, polyethylene glycol, acrylates, methacrylates, gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar, alginate, chitosan and acacia.

Typically, the chelating agent is selected from a group consisting of edetate disodium, edetate calcium disodium and edetate tetrasodium.

Typically, the buffering agent is at least one selected from a group consisting of acetic acid, adipic acid, benzoic acid, sodium benzoate, citric acid, lactic acid, maleic acid, potassium phosphate, sodium phosphate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium citrate, sodium tartarate, tartaric acid, sodium citrate dehydrate, sodium acetate trihydrate.

Typically, the surfactant is at least one selected from the group consisting of alkyl polyethylene oxide, alkylphenol polyethylene oxide, sodium laureth sulphate, sodium dodecyl sulphate, alkyl alcohol, sodium lauryl sulfate, polyoxyethylene/polyoxypropylene block polymers (poloxamers), glycerols, polyglycerols, fatty acids, polyethylene glycol hydroxystearate, polyalkyl glucosides, ceramides, polyethylene glycol/alkyl glycol copolymers, and polyethylene glycol/polyalkylene glycol ether di-block or tri-block copolymers, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, propylene glycol monostearate, macrogol esters, macrogol stearate, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, nonoxinols, octoxinols, tyloxapol, polyvinyl alcohols, polysorbate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate, sucrose esters, cetyl alcohol, oleyl alcohol, cetylpyridinium chloride, cetyl trimethylammonium bromide, tween 20 and tween 80.

Typically, the tonicity agent is at least one selected from a group consisting of glycerin, propylene glycol, polyethylene glycol, lactose, mannitol, dextrose, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium sulfate and sorbitol.

Typically, the pH adjusting agent is selected from a group consisting of sodium hydroxide, hydrochloric acid, triethanolamine, ammonia and mixtures thereof.

Typically, the vehicle is water for injection and said composition is in the form of a solution.

Typically, the vehicle is at least one ointment base selected from a group consisting of oil and wax and the ophthalmic composition is in the form of an ointment.

Typically, the oil is at least one selected from a group consisting of isopropyl myristate, myristyl myristate, isopropyl palmitate, isopropyl stearate, isopropyl oleate, n-butyl stearate, n-hexyl laurate, n-decyl oleate, isooctyl stearate, isononyl stearate, isononyl isononanoate, 2-ethylhexyl palmitate, 2-ethylhexyl laurate, 2-hexyldecyl stearate, 2-octyldodecyl palmitate, oleyl oleate, ethylhexyl cocoate, dicaprylyl carbonate, cetearyl isononanoate, oleyl erucate, erucyl oleate, erucyl erucate, octyldodecanol, polydecenes, squalane, dicaprylyl ether, triisostearine, butylene glycol dicaprylate/dicaprate, caprylic/capric triglyceride, olive oil, sunflower oil, soybean oil, peanut oil, rapeseed oil, almond oil, palm oil, coconut oil, palm karnel oil, caster oil, wheat germ oil, grape seed oil, thistle oil, silicon oils, lanolin oil, avocado oil and macadamia oil.

Typically, the wax is at least one selected from a group of candelilla wax, carnauba wax, bees wax, espartograss wax, cork wax, guaruma wax, rice germ oil wax, sugarcane wax, berry wax, ouricury wax, montan wax, jojoba wax, shea butter, beeswax, shellac wax, spermaceti, lanolin (wool wax), uropygial grease, ceresin, ozocerite (earth wax), paraffin waxes, sunflower wax, rlemon wax, grape fruit wax and laurel wax.

Typically, the vehicle comprises at least one polymer selected from a group consisting hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose, carbopol and the ophthalmic composition is in the form of a gel.

DETAILED DESCRIPTION OF THE INVENTION

The ophthalmic composition prepared in accordance with the present invention comprises 3-hydroxy-2,4,6-trimethylpyridine, pharmaceutically acceptable salts, esters, derivatives and polymorphs thereof in an amount in the range of about 0.05 to about 10 % of the mass of the composition, preservative in the range of about 0.005 to about 0.5% of the mass of the composition, stabilizer in the range of about 0.01 to about 1% of the mass of the composition, excipients in the range of about 0.02 to about 5 % of the mass of the composition and a vehicle, wherein pH of said ophthalmic composition is in the range of 4 to about 7.5.

The ophthalmic composition prepared in accordance with the present invention comprises the pharmaceutically acceptable salt of 3-hydroxy-2,4,6-trimethylpyridine is selected from a group of salts consisting of succinate, maleate, tartrate, oxalate, fumarate, citrate , hydrochloride, salicylate pamoate, hydrogen sulfate, sulfate methanesulphonate and benzenesulfonate.

The preservative used in the ophthalmic composition is at least one selected from a group consisting of benzalkonium chloride, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, chlorobutanol, metacresol, phenylmercuric nitrate, phenylmercuric acetate orphenylmercuric borate, thiomersal, myristylgamma picolonium chloride, phenol, benzoxonium chloride, cetrimide, phenyl ethanol, chlorohexidine and sodium perborate.

The stabilizer is selected from a group consisting of thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol, sodium edetate, creatinine, glycine, niacinamide, sodium acetyltryptophanate, sodium caprylate, sodium saccharin, citric acid and salts thereof.

The pharmaceutically acceptable excipients which used in the ophthalmic composition prepared in accordance with the present invention are selected from a group consisting of thickening agents, chelating agents, buffering agent, surfactants, tonicity agents, pH adjusting agents and solvents.

The ophthalmic composition preferably includes at least one thickening agent selected from a group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose, polyethylene glycol, acrylates, methacrylates, gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar, alginate , chitosan and acacia.

The ophthalmic composition prepared in accordance with the present invention includes chelating agent which is selected from a group consisting of edetate disodium, edetate calcium disodium and edetate tetrasodium.

In order to keep the pH of the ophthalmic composition within the effective and ophthalmologically safe range, at least one buffering agent is added. The buffering agent is selected from a group consisting of acetic acid, adipic acid, benzoic acid, sodium benzoate, citric acid, lactic acid, maleic acid, potassium phosphate, sodium phosphate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium citrate, sodium tartarate, tartaric acid, sodium citrate dehydrate, sodium acetate trihydrate.

The ophthalmic composition prepared in accordance with the present invention further includes at least one surfactant selected from the group consisting of alkyl polyethylene oxide, alkylphenol polyethylene oxide, sodium laureth sulphate, sodium dodecyl sulphate, alkyl alcohol, sodium lauryl sulfate, polyoxyethylene/polyoxypropylene block polymers (poloxamers), glycerols, polyglycerols, fatty acids, polyethylene glycol hydroxystearate, polyalkyl glucosides, ceramides, polyethylene glycol/alkyl glycol copolymers, and polyethylene glycol/polyalkylene glycol ether di-block or tri-block copolymers, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, propylene glycol monostearate, macrogol esters, macrogol stearate, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, nonoxinols, octoxinols, tyloxapol, polyvinyl alcohols, polysorbate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate, sucrose

esters, cetyl alcohol, oleyl alcohol, cetylpyridinium chloride, cetyl trimethylammonium bromide, tween 20 and tween 80.

The tonicity of the ophthalmic composition prepared in accordance with the present invention is adjusted to tonicity of lachrymal fluid by addition of tonicity agent.
The tonicity agent used in the ophthalmic composition to adjust the osmotic pressure is at least one selected from a group consisting of glycerin, propylene glycol, polyethylene glycol, lactose, mannitol, dextrose, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium sulfate and sorbitol.

Further, the pH of the ophthalmic composition is adjusted in the range of about 4 to about 7.5 to prevent eye irritation. The pH adjusting agent is selected from a group consisting of sodium hydroxide, hydrochloric acid, triethanolamine, ammonia and mixtures thereof.

In accordance with one of the embodiment of the present invention, an ophthalmic composition is in the form of a solution and the vehicle used to prepare an ophthalmic solution is water for injection.

In accordance with another embodiment of the present invention, an ophthalmic composition is in the form of an ointment and the vehicle used to prepare an ophthalmic ointment is at least one ointment base selected from a group consisting of oil and wax.

The oil is at least one selected from a group consisting of isopropyl myristate, myristyl myristate, isopropyl palmitate, isopropyl stearate, isopropyl oleate, n-butyl stearate, n-hexyl laurate, n-decyl oleate, isooctyl stearate, isononyl stearate, isononyl isononanoate, 2-ethylhexyl palmitate, 2-ethylhexyl laurate, 2-hexyldecyl stearate, 2-octyldodecyl palmitate, oleyl oleate, ethylhexyl cocoate, dicaprylyl carbonate, cetearyl isononanoate, oleyl erucate, erucyl oleate, erucyl erucate, octyldodecanol, polydecenes, squalane, dicaprylyl ether, triisostearine, butylene glycol dicaprylate/dicaprate, caprylic/capric triglyceride, olive oil, sunflower oil,

soybean oil, peanut oil, rapeseed oil, almond oil, palm oil, coconut oil, palm karnel oil, caster oil, wheat germ oil, grape seed oil, thistle oil, silicon oils, lanolin oil, avocado oil and macadamia oil.

The wax is at least one selected from a group of candelilla wax, carnauba wax, bees wax, espartograss wax, cork wax, guaruma wax, rice germ oil wax, sugarcane wax, berry wax, ouricury wax, montan wax, jojoba wax, shea butter, beeswax, shellac wax, spermaceti, lanolin (wool wax), uropygial grease, ceresin, ozocerite (earth wax), paraffin waxes, sunflower wax, rlemon wax, grape fruit wax and laurel wax.

In accordance with still another embodiment of the present invention, an ophthalmic composition is in the form a gel and the vehicle used to prepare an ophthalmic gel in accordance with the present invention is at least one polymer selected from a group consisting hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose and carbopol.

Following examples illustrate the invention, but are not intended to limit the scope of the present invention.

Ophthalmic formulations, in accordance with the present invention employing different salts of 3-hydroxy-2, 4, 6-trimethylpyridine were prepared in the form of solution, gel and ointment.

Example 1

3-hydroxy-2,4,6-trimethylpyridine succinate solution

A solution of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-Hydroxy-2, 4, 6-trimethylpyridine succinate	- 1.0%
Benzylkonium chloride	- 0.01%
Hydrochloric acid	- QS
Sodium hydroxide	- QS
Potassium monobasic phosphate	- QS
Dibasic sodium phosphate	- QS

HPMC 15cps	-0.50%
Water for injection	- QS

3-hydroxy-2,4,6-trimethylpyridine succinate and other ingredients were dissolved in water for injection. The pH of the solution was adjusted to 6. The resultant solution was sterilized and aseptically filled into vials.

Example 2

A solution of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2,4,6-trimethylpyridine succinate	- 1.0%
Benzalkonium chloride	- 0.01%
Hydrochloric acid	- QS
Sodium hydroxide	- QS
Sodium benzoate	- 0.15%
Potassium monobasic phosphate	- QS
Dibasic sodium phosphate	- QS
HPMC 15cps	- 0.50%
Water for injection	- QS

Example-3

A solution of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2,4,6-trimethylpyridine succinate	- 1.0%
Benzalkonium chloride	- 0.01%
Sodium chloride	- 0.06%
Hydrochloric acid	- QS
Sodium hydroxide	- QS
Potassium monobasic phosphate	- QS
Dibasic sodium phosphate	- QS
Water for injection	- QS

Example 4

A solution of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2,4,6-trimethylpyridine succinate	- 1.0%
Benzalkonium chloride	- 0.01%
EDTA	- 0.05%
Mannitol	- 2.9 %
Sodium acetate	- QS
Glacial acetic acid	- QS
Hydrochloric acid	- QS
Sodium hydroxide	- QS
Water for injection	- QS

Example 5

A solution of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2,4,6-trimethylpyridine succinate	1.0%
Benzalkonium chloride	0.01%
EDTA	0.05%
Mannitol	2.0%
Sodium chloride	0.2%
Hydrochloric acid	Qs
Sodium hydroxide	Qs
HPMC (15cps)	0.50%
Water for injection	QS

Example 6

A gel of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2, 4, 6-trimethylpyridine succinate	1.0%
Carbopol 934P	2%
Triethanolamine	QS

Benzalkonium chloride	QS
Water for injection	QS

Carbopol 934P was dispersed in water for injection and stirred for 1 hour. Resultant dispersion was kept for soaking for 10 hours to form a clear gel. To this 3-hydroxy-2, 4, 6-trimethylpyridine succinate dissolved in water for injection was added with continuous stirring. Further, benzalkonium chloride was added and stirred for 10 minutes. Finally, triethanolamine was added and pH of the gel was adjusted to 5.9.The formulation was sterilized and aseptically filled into the tubes.

Example 7

An ointment of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-hydroxy-2,4,6-trimethylpyridine succinate	1.0%
White soft paraffin	80.0%
Liquid paraffin	5.0%
Cetsteryl alcohol	5.0%
Hard paraffin	5.0%
Benzalkonium chloride	QS
Buffer	QS
Water for injection	QS

The ointment base was prepared by melting together white soft paraffin, liquid paraffin, cetsteryl alcohol and hard paraffin. To this base, 3-hydroxy-2, 4, 6-trimethylpyridine succinate and benzalkonium chloride dissolved in water for injection were added and homogeneously blended. The pH of the ointment was adjusted to 5.8. The ointment was sterilized and aseptically filled into the tubes.

Example 8

An ointment of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-Hydroxy-2, 4, 6-trimethylpyridine succinate	1.0%
White soft paraffin	65.0%

Liquid paraffin	10.0%
Cetsteryl alcohol	7.0%
Hard paraffin	12.0%
Benzalkonium chloride	QS
Buffer	QS
Water for injection	QS

Example 9

An ointment of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-Hydroxy-2, 4, 6-trimethylpyridine succinate	1.0%
White Soft Paraffin	65.0%
Hard paraffin	5.0%
Liquid Paraffin	25.0%
Preservative	QS
Buffer	QS
Water for injection	QS

Example 10

An ointment of 3-hydroxy-2,4,6-trimethylpyridine succinate was formulated as follows:

3-Hydroxy-2,4,6-trimethylpyridine succinate	1.0%
White Soft Paraffin	67.0%
Liquid Paraffin	29.0%
Preservative	QS
Buffer	QS
Water for injection	QS

Preclinical trials:

The efficiency of the ophthalmic composition comprising 3-hydroxy-2,4,6-trimethylpyridine prepared in accordance with the present invention, in traumatic

hemophthalmia, on the basis of the modern ultrasonic researches of eyeglobe (eyeball) and parameters of biochemical researches of blood serum, tear liquid, liquid of the anterior chamber and eye tissue was studied.

Material and methods:

Studies were carried out in 12 chinchilla rabbits having body weight 2.0-2.5 kg. A traumatic hemophthalmia was modeled by introduction of 0.5 to 0.7 ml of autoblood into a vitreous body through a puncture in a sclera on distance of 5 mm from a limbus, under a local anaesthesia. The basic group made with 6 rabbits (12 eyes), daily received a formulation prepared in accordance with the present invention parabulbarly (0.5 ml of 1 % solution). A control group presented by 6 animals (12 eyes), daily received parabulbar emoxipin (2-ethyl-6-methyl-3-hydroxypiridin) in the same dosage. Treatment was carried out within 14 days after a trauma.

Besides the traditional ophthalmologic examination such as biomicroscopy, direct and indirect ophthalmoscopy, all the animals passed through ultrasonic scanning of an eye by means of the device " Voluson 730 " ("Kretz"). The studies were carried out on the 1, 3, 7, 10 and 14^{th} day of the experiment. For the estimation of efficiency of the treatment following tests were used: density, area, volume of a hemophthalmia and opportunity (possibility) of ophthalmoscopy of an eye ground. Density of a hemophthalmia was estimated in standard (conventional) units of density (SUD), 100 SUD were accepted for the maximal value, corresponding to the ultrasonic sclera density. Depending on the degree of acoustic density of a hemophthalmia, a high (100 - 50 SUD), medium (50 - 25 SUD) and low (less than 25 SUD) densities were distinguished. To determine the hemophthalmia the area measurement in sm^2 was used. The volume of the intraocular hemorrhage was studied with the help of 3D modelling in the B-regimen of a grey scale and measurement in sm^3.

At the ultrasonic examination of the intact rabbit's eyes, the average volume of vitreous body (1.0 ± 0.9 sm^3) and the average area of a vitreous body (1.04 ± 0.8 sm^2)

were fixed. Proceeding from the obtained data, the total hemophthalmia (from 100 up to 50 % of the vitreous body volume) was equated to the volume of 0.5-1.0 sm^3 and of 0.5-1.0 sm^2, a wide-spread hemophthalmia (50 - 25 % of volume of a vitreous) corresponded to the area of 0.5-0.25 sm^3 , both 0.5-0.25 sm^2, and the partial hemophthalmia occupied up to 0.25 sm^3 and 0.25 sm^2 (up to 25 % of the vitreous volume).

Capability of the eyeground ophthalmoscopy was estimated by a 3-mark(point) scale depending on the image sharpness (0 - ophthalmoscopy is impossible (not capable), 3 - details of an eyeground are clearly visible).

The materials used for biochemical examination were as follows: blood, liquid of the anterior chamber, tear liquid, tunics of eyeglobe (retina, a vitreous body). The blood was taken from the aural vein in an amount of 3 ml. Sampling of tear liquid was carried out by a microcapillary after instillation of distilled water into the conjunctival cavity. Liquid of the anterior chamber was obtained by paracentesis. The blood sampling as well as liquid of the anterior chamber and teat liquid were carried out on the 1^{st}, 7^{th} and 14^{th} day of the experiment. On the 15^{th} day of the studies, the animals were killed (pithed) by air embolism and both the eyes were enucleated. The eyes were prepared by tunic separation. Retina and vitreous body were obtained.

For estimation of activity of the preparations the concentration of products of the free radical oxidation, active in the reaction with thiobarbituric acid (TBA-active products), protein concentration, and the antioxidant activity (AOA) were determined.

Results:

The data of preclinical and ultrasonic examinations at the experimental hemophthalmia in dynamics is shown in Table No. 1.

Table 1: Dynamics of parameters of preclinical and ultrasonic examination at the experimental hemophthalmia in the basic (A) and control (B) groups.

Day	Parameters							
	Volume of a hemophthalmia, sm^3		Area of hemophthalmia, sm^2		Density of hemophthalmia, SUD		Capability of ophthalmoscopy and eyeground, points	
	A	B	A	B	A	B	A	B
1st	0.53±0.4	0.54±0.8	0.49±0.7	0.48±0.5	84±2.4	82±1.4	1.5	1.5
3rd	0.78±0.2	0.81±0.8	0.74±0.9	0.76±0.1	72±3.1	76±2.6	0-0.5	0-0.5
7th	0.51±0.6	0.7±0.1	0.47±0.4	0.68±0.9	49±1.4	65±2.1	1.5	0.8
10th	0.24±0.1	0.53±0.4	0.2±0.1	0.5±0.2	23±1.1	48±1.5	2.2	1.6
14th	0.15±0.2	0.4±0.7	0.11±0.7	0.39±0.4	13±0.6	32±0.8	2.8	2.0

In the first day of experiment, the parameters of ultrasonic and clinical examination were practically identical in all groups: the density of hemophthalmia in average made from 81 up to 85 SUD, the area – 0.52-0.55 sm^2, the volume 0.47-0.5 sm^3, the capability of ophthalmoscopy of an eyeground was corresponded to 1-2 points. Thus, in all animals the intraocular hemorrhage which complicated the capability of ophthalmoscopy of an eyeground was marked rather small in volume, but essential in density.

By the 3rd day of studies the blood was regularly distributed in a vitreous body, thus the density of hemophthalmia was decreased a little. The area and the volume of a hemorrhage were corresponded to criteria of the total hemophthalmia (about 80 % of a vitreous body), the density remained high (more than 70 SUD), the eye ground practically was not looked through (seen) (0 – 0.5 points). Since from the 3rd day of experiment the tendency to the faster resorption of hemorrhage of rabbits of the basic group was outlined, however, no statistically significant difference of ultrasonic examination was observed. To characterize clinical current of the given period it is necessary to refer the more expressed reaction of an eye to a trauma in animals of the control group in comparison with the experienced group

(lacrimation, photophobia, injection of an eyeglobe, liquid opalescence of the anterior chamber).

By the 7th day, the difference of preclinical and ultrasonic parameters of a hemophthalmia became more noticeable. In the basic group, the area of a hemophthalmia was decreased up to 0.51 ±0.6 sm^2, volume up to 0.47±0.4 sm^3, density up to 49±1.4 SUD; capability of the eyeground ophthalmoscopy was equal to 1.5 points. In the basic group the wide-spread hemophthalmia of average density was observed. In the control group, the tendency to resorption of a hemorrhage was less expressed: the area of a hemophthalmia was 0.7±0.1 sm^2, volume 0.68±0.9 sm^3, density 65±2.1 SUD, capability of the eyeground ophthalmoscopy was 1 point. Thus, in animals of the control group the clinical picture practically did not changed.

By the 10th day, in the basic group the hemophthalmia was completely resolved in two animals, in other cases marked a noticeable decrease of the area (0.24±0,1sm^2), volume (0.2±0.1 sm^3) and density (23±1.1 SUD) of hemorrhage, the eyeground (2.2 points) was well seen. The intraocular hemorrhage corresponded to a partial hemophthalmia with a low density. In the control group the effect of treatment was less expressed: the area of a hemophthalmia averaged to 0.53±0.4 sm^2, volume 0.5±0.2 sm^3, density 48±1.5 SUD, capability of the eyeground ophthalmoscopy was equal to 1.8 points. On the 10th day of the studies, some rabbits receiving emoxipin had the tendency of sheet-anchor formation in a vitreous body.

On the 14th day the hemophthalmia was completely resolved in 50 % of animals in the basic group, the area, volume and density (0.15±0.2 sm^2, 0.11±0.7 sm^3 and 13±0.6 SUD, accordingly) of hemorrhage were considerably decreased, the eyeground (2.6 points) was well seen in the other animals. In the control group, the result of the treatment appeared less expressed: the area of a hemophthalmia was 0.47±0.7 sm^2, volume 0.39±0.4 sm^3, density 32±0.8 SUD, the ophthalmoscopy picture of an eyeground was not clear (2 points). In the control group, no noticeable changes were obtained in comparison with the 10th day; the phenomena of fibrosis and sheet-anchor formation in a vitreous body were marked in 30 % of animals.

Table No.2 shows biochemical parameters in blood serum (BS), tear liquid (TL) and the anterior chamber liquid (ACL) at an experimental hemophthalmia in the basic (A) and the control (B) groups.

Table 2: Biochemical parameters

	Protein concentration (mg / ml)		Concentration of TBA-active products (nmol/ml)		AOA (relative unit)	
	A	B	A	B	A	B
1st day						
BS	90.0 ± 6.0	85.2 ± 0.9	1.29 ±0.13	2.53 ± 0.28	1.7 ±0.3	1.5±0.2
TL	0.32 ± 0.2	0.35 ±0.1	0.14 ±0.01	0.16 ±0.02	0.23± 0.02	0.13 ± 0.03
ACL	3.1 ± 1.2	3.9 ±1.0	0.97±0.18	1.6 ± 0.3	0.4± 0.01	0.33± 0.02
7th day						
BS	82.4 ± 1.3	103.0 ± 5.0	1.17 ±0.05	2.4 ± 0.09	2.4± 0.02	1.8 ±0.07
TL	0.7 ± 0.2	0.91±0.25	0.13 ±0.05	0.46± 0.07	0.24 ± 0.02	0.18 ±0.05
ACL	4.4 ±1.2	10.0 ± 3.0	0.8 ± 0.5	2.2 ± 0.4	0.8± 0.07	0.55 ± 0.04
14th day						
BS	47.0 ± 3.0	73.0 ±2.0	0.9±0.15	1.6 ±0.2	1.9 ±0.7	1.3 ±0.3
TL	0.6 ± 0.2	0.74 ±0.14	0.04± 0.07	0.3 ± 0.2	0.08± 0.02	0.06± 0.03
ACL	4.1 ±1.1	5.5 ±1.0	0.6 ±0.2	2.2 ± 0.3	0.5± 0.05	0.33± 0.06
Retina					0.4 ± 0.07	0.23 ± 0.08
Vitreous body					3.5 ±0.9	1.6 ±0.7

From the mentioned data it is evident that the protein concentration in the 1st day of experiment, and AOA in all biological liquids practically did not varied in the groups. Concentration of TBA-active products in the blood serum had no essential differences either, however, in the tear and anterior chamber liquid of the rabbits of the basic group, the concentration of TBA-active products was lower than that in the rabbits of the control group.

The greatest difference in biochemical parameters observed on the 7-th day of experiment and coincided with the beginning of the active hemorrhage resorption in rabbits of the basic group. In animals of the basic group AOA was in the average 1.5 times higher than in the control group in all measured substrata: in the blood serum 2.4±0.02 - 1.8±0.07/100 mcl, tear liquid 0.24±0.02-0.18±0.05/200 mcl and in the anterior chamber liquid 0.8±0.07 - 0.55±0.04/100 mcl. On the contrary, concentration of TBA-active products was grown in the control group (2.4±0.09 nmol/ml in the blood serum, 0.46±0.07 nmol/ml in the tear liquid, 2.2±0.4 nmol/ml in the anterior chamber liquid), and was reduced in the basic group (1.17±0.05 nmol/ml in the blood serum, 0.13±0.05 nmol/ml in the tear liquid, 0.8±0.5 nmol/ml in the anterior chamber liquid). Similar changes were observed at examination of protein concentration in the blood serum in rabbits of the control (103.0 ±5.0 mg / ml) and the basic (82.4±1.3 mg / ml) groups. In all animals the protein concentration was grown in the tear and the anterior chamber liquid on the 7th day.

By the 14-th day of experiment, statistically significant differences in the biochemical parameters were marked. In both groups, AOA was insignificantly reduced, however the higher parameters were in the animals receiving formulation prepared in accordance with the present invention (1.9±0.7/100 mcl in the blood serum, 0.08±0.02/200 mcl in the tear liquid, 0.5±0.05/100 mcl in the anterior chamber liquid), and the lower parameters were in the animals receiving emoxipin (1.3±0.03/100 mcl in the blood serum, 0.06±0.03/200 mcl in the tear liquid, 0.33±0.06/100 mcl in the anterior chamber liquid). Concentration of TBA-active products was also decreased in all rabbits, thus in the basic group their values were lower, than in the control group (0.9±0.15 - 1.6±0.2 nmol/ml in the blood serum, 0.04±0.07 - 0.3±0.2 nmol/ml in the tear liquid, 0.6±0.2 - 2.2±0.3 nmol/ml in the anterior chamber liquid, accordingly). Similar changes were marked at the examination of parameters of protein concentration in both the groups of animals.
In AOA studies the augmentation of the given parameter was observed in 2 times in the eye tunics, a retina and a vitreous body, in rabbits of the basic group in comparison with the control group.

Conclusions:

1. The ophthalmic composition prepared in accordance with the present invention renders a positive effect on the resorptive processes in a vitreous body at the experimental traumatic hemophthalmia.
2. On the basis of parameters of clinical and ultrasonic examination of eyes of the experimental animals at the traumatic hemophthalmia in dynamics, it is established that efficiency of the composition prepared in accordance with the present invention is much higher in comparison with emoxipin.
3. Results of biochemical studies of the blood serum, tear liquid, the anterior chamber liquid and eye tissues (*in vivo*) shows that the composition prepared in accordance with the present invention has higher antioxidant activity than emoxipin.

ANECDOTAL TRIALS:

Dramatic and significant results have been obtained in individual anecdotal cases of patients presenting with ischemia, intraocular hemorrhage and macular degeneration in which the condition is either reversed or ameliorated.
The applicant craves leave to submit formal data to establish significant enhancement of efficacy by way of explanation to support these preliminary findings.

While considerable emphasis has been placed herein on the specific ingredients of the preferred formulation, it will be appreciated that many additional ingredients can be added and that many changes can be made in the preferred formulation without departing from the principles of the invention. These and other changes in the preferred formulation of the invention will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the invention and not as a limitation.

Claims:

1. An ophthalmic composition comprising 3-hydroxy 2, 4, 6 trimethylpyridine, pharmaceutically acceptable salts, esters, derivatives and polymorphs thereof in an amount in the range of about 0.05 to about 10 % of the mass of the composition, preservative in the range of about 0.005 to about 0.5% of the mass of the composition, stabilizer in the range of about 0.01 to about 1% of the mass of the composition, excipients in the range of about 0.02 to about 5 % of the mass of the composition and a vehicle, wherein pH of said ophthalmic composition is in the range of about 4 to about 7.5.

2. The ophthalmic composition as claimed in claim 1, wherein the pharmaceutically acceptable salt of 3-hydroxy-2,4,6-trimethylpyridine is selected from a group of salts consisting of succinate, maleate, tartrate, oxalate, fumarate, citrate, hydrochloride, salicylate, pamoate, hydrogen sulfate, sulfate methanesulphonate and benzenesulfonate.

3. The ophthalmic composition as claimed in claim 1, wherein the preservative is at least one selected from a group consisting of benzalkonium chloride, benzyl alcohol, methyl paraben, propyl paraben, butyl paraben, chlorobutanol, metacresol, phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, thiomersal, myristylgamma picolonium chloride, phenol, benzoxonium chloride, cetrimide, phenyl ethanol, chlorohexidine and sodium perborate.

4. The ophthalmic composition as claimed in claim 1, in which the stabilizer is selected from a group consisting of thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol, sodium edetate, creatinine, glycine, niacinamide, sodium acetyltryptophanate, sodium caprylate, citric acid and salts thereof.

5. The ophthalmic composition as claimed in claim 1, wherein the excipients are selected from a group consisting of thickening agents, chelating agents, buffering agent, surfactants, tonicity agents, pH adjusting agents and solvents.

6. The ophthalmic composition as claimed in claim 5, wherein the thickening agent is at least one selected from a group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose, polyethylene glycol, acrylates, methacrylates, gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenin, agar, alginate, chitosan and acacia.

7. The ophthalmic composition as claimed in claim 5, wherein the chelating agent is selected from a group consisting of edetate disodium, edetate calcium disodium and edetate tetrasodium

8. The ophthalmic composition as claimed in claim 5, wherein the buffering agent is at least one selected from a group consisting of acetic acid, adipic acid, benzoic acid, sodium benzoate, citric acid, lactic acid, maleic acid, potassium phosphate, sodium phosphate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium citrate, sodium tartarate, tartaric acid, sodium citrate dehydrate and sodium acetate trihydrate.

9. The ophthalmic composition as claimed in claim 5, wherein at least one surfactant is selected from the group consisting of alkyl polyethylene oxide, alkylphenol polyethylene oxide, sodium laureth sulphate, sodium dodecyl sulphate, alkyl alcohol, sodium lauryl sulfate, polyoxyethylene block polymers, polyoxypropylene block polymers (poloxamers), glycerols, polyglycerols, fatty acids, polyethylene glycol hydroxystearate, polyalkyl glucosides, ceramides, polyethylene glycol/alkyl glycol copolymers, and polyethylene glycol/polyalkylene glycol ether di-block or tri-block copolymers, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, propylene glycol monostearate, macrogol esters, macrogol stearate, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, nonoxinols, octoxinols, tyloxapol, polyvinyl alcohols, polysorbate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate ,

sucrose esters, cetyl alcohol, oleyl alcohol, cetylpyridinium chloride, cetyl trimethylammonium bromide, tween 20 and tween 80.

10. The ophthalmic composition as claimed in claim 5, wherein the tonicity agent is at least one selected from a group consisting of glycerin, propylene glycol, polyethylene glycol, lactose, mannitol, dextrose, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium sulfate and sorbitol.

11. The ophthalmic composition as claimed in claim 5, wherein the pH adjusting agent is selected from a group consisting of sodium hydroxide , hydrochloric acid, triethanolamine, ammonia and mixtures thereof.

12. The ophthalmic composition as claimed in claim 1, wherein the concentration of 3-hydroxy 2, 4, 6 trimethylpyridine is in the range of about 0.5 to about 3 % of the total mass of the composition.

13. The ophthalmic composition as claimed in claim 1, wherein the vehicle is water for injection and said composition is in the form of a solution

14. The ophthalmic composition as claimed in claim 1, wherein the vehicle is at least one ointment base selected from a group consisting of oil and wax and the ophthalmic composition is in the form of an ointment.

15. The ophthalmic composition as claimed in claim 14, wherein the oil is at least one selected from a group consisting of isopropyl myristate, myristyl myristate, isopropyl palmitate, isopropyl stearate, isopropyl oleate, n-butyl stearate, n-hexyl laurate, n-decyl oleate, isooctyl stearate, isononyl stearate, isononyl isononanoate, 2-ethylhexyl palmitate, 2-ethylhexyl laurate, 2-hexyldecyl stearate, 2-octyldodecyl palmitate, oleyl oleate, ethylhexyl cocoate, dicaprylyl carbonate, cetearyl isononanoate, oleyl erucate, erucyl oleate, erucyl erucate, octyldodecanol, polydecenes, squalane, dicaprylyl ether, triisostearine, butylene glycol dicaprylate/dicaprate, caprylic/capric triglyceride, olive oil, sunflower oil, soybean oil, peanut oil, rapeseed oil, almond oil, palm oil, coconut oil, palm

karnel oil, caster oil, wheat germ oil, grape seed oil, thistle oil, silicon oils, lanolin oil, avocado oil and macadamia oil.

16. The ophthalmic composition as claimed in claim 14, wherein the wax is at least one selected from a group of candelilla wax, carnauba wax, bees wax, espartograss wax, cork wax, guaruma wax, rice germ oil wax, sugarcane wax, berry wax, ouricury wax, montan wax, jojoba wax, shea butter, beeswax, shellac wax, spermaceti, wool wax, uropygial grease, ceresin, ozocerite, paraffin waxes, sunflower wax, rlemon wax, grape fruit wax and laurel wax.

17. The ophthalmic composition as claimed in claim 1, wherein the vehicle comprises at least one polymer selected from a group consisting ethyl cellulose, methyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxy methyl cellulose, hydroxyethyl cellulose, carbopol and the ophthalmic composition is in the form of a gel.