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(71) Applicant: **VID D.O.O.** [SI/SI]; Ulica Vinka Vodopivca
21, 5000 Nova Gorica (SI).

(72) Inventors: **FEINBAUM, Claes G.**; Badhusgatan 13, S-
261 30 Landskrona (SE). **PATEL, Sudhir**; Netherton
Farm, Thornhill, Stirling Scotland FK8 3QQ (GB). **ŠAL-**
AMUN, Franc; Temnica 10f, 5296 Kostanjevica na Krasu
(SI).

(74) Agent: **PIPAN, Marjan**; Kotnikova 5, 1000 Ljubljana
(SI).

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(54) Title: PHARMACOLOGICAL OPHTHALMIC COMPOSITION FOR USE IN THE CORRECTION OF PRESBYOPIA AND ITS ADMINISTRATION

(57) Abstract: The object of the invention is to provide a pharmacological ophthalmic composition for use in the correction of presbyopia as a drop introduced onto the surface of the eye and surrounding soft tissue (drops) or as an implant surgically introduced into the subconjunctival space with sustained slow release application.



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PHARMACOLOGICAL OPHTHALMIC COMPOSITION FOR USE IN THE CORRECTION OF PRESBYOPIA AND ITS ADMINISTRATION

The object of the invention is to provide a pharmacological ophthalmic
5 composition for use in the correction of presbyopia as a drop introduced
onto the surface of the eye and surrounding soft tissue (drops) or as an
implant surgically introduced into the eye with sustained slow release
application. With drops, or implant, a reduction of pupil size is achieved,
leading to an increase in depth of field, a fall in the magnitude of the
10 ocular high order optical aberrations and improved near and distance
unaided visual acuity. The invention belongs to class A 61K45/06, A61K
31/4178 and A61P 27/10 of international patent classification.

When a young emmetrope fixates on a near object two main changes
occur in the eye: accommodation and miosis. Accommodation is a change
15 in crystalline lens refractive power. Lens becomes rounder, by which its
refractive power increases. Miosis is a decrease in pupil size by which
depth of focus increases and high order aberrations decrease.

Both, miosis and accommodation occur under the influence of the
parasympathetic nervous system. Parasympathomimetic, acetylcholine,
20 binding to muscarinic receptors, induces muscular contraction of the ciliary
muscle and the sphincter of the pupil.

Presbyopia is decreasing age-related ability to focus on objects at close
distances because of a gradual loss of accommodative amplitude. Soon

after the age of fifty, lens loses all its ability to undergo accommodative optical changes. Measured subjectively, there is a progressive loss of accommodative amplitude until about the age of fifty, where it remains at about 1 diopter. This is depth of focus due to aberrations and miosis,
5 defined as pseudo accommodation.

Presbyopia has been corrected with the use of spectacles, contact lenses or intra-ocular implants, and corneal ablation or inlays. The surgical methods that have been proposed to correct presbyopia do not completely restore the natural accommodative functionality of the eye that has been
10 reduced either by natural ageing or by other means. Pharmacological treatments have been proposed to restore the natural loss of the accommodative functionality of the eye that leads to presbyopia. According to EP 1 938 839, a combination of parasympathomimetics and non-steroidal anti-inflammatory agents where the parasympathomimetic in
15 use is pilocarpine (or its salts) in concentration from 1% to 2%. These concentrations of the parasympathomimetic can lead to undesirable side effects.

It is also known that delivery of an ophthalmic composition with sustained-release by way of an intravitreal microinsert near the base of
20 the eye is efficient and advantageous. Such treatment is described in the WO 2011/079123 A1 document (description of the procedure set out in the attached pat. document (WO2011/079123 A1). The advantage of the microinsert is that the slowly released ingredients remain in the eye, are

not lost via the natural drainage channels associated with fluids introduced onto the ocular surface. The microinsert saves the user (patient) time and effort by avoiding repeat instillation of drops every so often. The present invention relates to the ophthalmic composition for use in the correction of presbyopia without harmful influences as stated in the the other documents.

Ophthalmic composition according to the invention contains the following: Sodium Hyaluronate from 0.1% to 0.9%, Diclofenac Sodium from 0.006% to 0.012% and Pilocarpine Hydrochloride from 0.2% to 0.4%. The composition of the invention extends to encompass other constituents that may be added, modified, substituted or removed to improve comfort and overall efficacy.

The modus operandi of the invention is as follows.

The size of the pupil reduces as a consequence of the action of the constituents of the drop on the muscle fibres of the natural iris. Inducing miosis, depth of focus increases and the magnitude of high order aberrations decrease, improving uncorrected near and distance visual acuity.

The advantage of the composition is i) the low dosage ii) anti-inflammatory action iii) comfort. A literature search does not reveal any known long term harmful effects of any of the constituents in the noted concentrations on the eye. This is supported by our observations based on over 100 cases (62 subjects).

The drops are proposed for use on persons of generally good health with small distance optical prescriptions, those that previously had laser eye surgery of the cornea (LASIK or PRK), those that previously had routine cataract surgery and implanted with standard monofocal intra-ocular implant lens. One or two drops are introduced onto the ocular surface, the improvement in distance and near vision is normally reported after a few minutes and the effect can last up to 8 hours.

The slow release implant is surgically introduced into subconjunctival space by an ophthalmic surgeon after s/he has decided that the patient would benefit from the implant following provocative testing using the topical drops. The constituents passively reach the iris, interact with the muscle fibres of the iris changing the size of the pupil. This action leads to an increase in depth of field and improvement in the distance and near vision as noted herein.

PATENT CLAIMS

1. Pharmacological ophthalmic composition for the correction of
5 presbyopia comprising Sodium Hyaluronate from 0.1% to 0.9%,
Diclofenac Sodium from 0.006% to 0.012% and Pilocarpine
Hydrochloride from 0.2% to 0.4%.
2. The use of pharmacological ophthalmic composition according to claim
10 1, wherein it is to be administered in a form of one to two drops during a
period of 8 hours onto the ocular surface.
3. The use of pharmacological ophthalmic composition according to claim
1, wherein it is to be administered in a form of the sustained slow
15 release implant, surgically introduced into subconjunctival space.

INTERNATIONAL SEARCH REPORT

International application No
PCT/SI2014/000008

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/196 A61K31/4178 A61K31/728 A61P27/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 938 839 A1 (BENOZZI JORGE LUIS [AR]) 2 July 2008 (2008-07-02) cited in the application claims 1, 2, 4, 5 ----- -/--	1-3



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Terenzi, Carla

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAMBER O ET AL: "SODIUM HYALURONATE AS AN OPHTHALMIC VEHICLE: SOME FACTORS GOVERNING ITS EFFECT ON THE OCULAR ABSORPTION OF PILOCARPINE", CURRENT EYE RESEARCH, IRL PRESS, OXFORD, GB, vol. 8, no. 6, 1 January 1989 (1989-01-01) , pages 563-567, XP009001243, ISSN: 0271-3683 abstract page 566, right-hand column, line 5 - line 15 page 567, left-hand column, line 1 - line 4	1-3
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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