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(54) Title: COMPOSITION OF GLYCOSAMINOGLYCAN AND A PEROXIDE FOR THE TREATMENT OF DRY EYE

(57) Abstract: The present invention relates to ophtalmic pharmaceutical compositions for treatment of dry eye symptoms compris-
ing a hyaluronate stabilized and hydrogen peroxide, and a method of treating dry eye symptoms.



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COMPOSITION OF GLYCOSAMINOGLYCAN AND A PEROXIDE FOR THE TREATMENT OF DRY EYE

The present invention relates to ophthalmic pharmaceutical compositions for treatment of dry eye symptoms comprising a hyaluronate and a method of treating dry eye symptoms with said compositions.

Dry eye, also known as or keratoconjunctivitis sicca (KCS) and dyslacrima, refer to, or are a component of, a variety of disorders that results from any condition or circumstance that decreases tear secretion or increases tear film evaporation. Patients suffering from dry eye may experience symptoms such as e.g. foreign body sensation, burning, ocular itching, ocular inflammation, persistent irritation, feeling of dryness and hyperemia. In severe cases, dry eye can seriously impair a person's vision. Dry eye results in a breakdown of the pre-ocular tear film which commonly results in dehydration of the exposed outer surface and hence the symptoms described above.

Dry eye symptoms may be treated by administering, e.g. instilling, artificial tears to the eye in order to supplement the ocular tear film. Examples of tear substitutes are disclosed e.g. in US 5,209,927, US 5,294,607 and US 4,409,205 which are incorporated herein by reference.

It is desirable to develop an ophthalmic multidose composition that will better alleviate the symptoms of dry eye and is safe. Excellent antimicrobial preservation, preferably as defined as European Pharmacopeia (Eur. Ph.) criteria A for ophthalmic preparations, e.g. as described in Eur. Ph. Supplement 2001, Section 5.1.3, page 293 to 295, is required. E.g. in the case of bacteria e.g. after 6 hours, 99.0% of microorganisms and after 24 hours, 99.9% of microorganisms and after 28 days, 100% of microorganisms have to be killed relative to the initial concentration of microorganisms. E.g. in the case of fungi, e.g. after 7 days, 99.0% of microorganisms and after 28 days, more than 99.0% of microorganisms have to be killed relative to the initial concentration of microorganisms. The initial concentration of microorganisms is e.g. 100 000 to 1 million microorganisms per ml or per gram. Accordingly, the present invention provides for ophthalmic compositions for treatment of dry eye symptoms which compositions meet the criteria A requirements for efficacy of antimicrobial preservation of the Eur. Ph. (Eur. Ph. Supplement 2001, Section 5.1.3) for ophthalmic preparations.

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EP 354 186 discloses a method of preserving ophthalmic solutions having a hydrogen peroxide content of about 0.001% to about 0.1% by weight. Applicants have found that compositions comprising

- (i) glycosaminoglycans and
- (ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight based on the total weight of composition

meet the criteria A requirements for efficacy of antimicrobial preservation of the Eur. Ph. (Eur. Ph. Supplement 2001, Section 5.1.3) for ophthalmic preparations, are particularly well tolerated and do not irritate the eye.

The glycosaminoglycan is preferably e.g. hyaluronic acid, hylan, hylaluronan, heparin, heparan sulphate, chondroitin sulfate, keratin sulphate or dermatan sulphate or ophthalmically acceptable salts thereof, or mixtures thereof, preferably hyaluronic acid, hyaluronan derivatives or an ophthalmically acceptable salt thereof. The glycosaminoglycan may be present e.g. in an amount of 0.05 to 5%, preferably 1 to 4% by weight based on the total weight of composition.

Hyaluronic acid (Fiedler, H.P.; 1996; Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Editio Cantor Verlag Aulendorf (Germany), p. 763) is e.g. known and commercially available from Vitrolife AB, Sweden, or from Pentapharm AG, Switzerland, e.g. under the names hyaluronic acid Pentapharm or hyaluronic acid BT. Preferably, hyaluronic acid is in form of its alkali salts, preferably sodium hyaluronate. Hyaluronic acid may be obtained e.g. from cocks combs or may be manufactured biotechnically. The preferred molecular weight of the hyaluronate is e.g. above about 750'000 Daltons to e.g. below about 4 million Daltons, more preferred from about 1 million Daltons to about 3.5 million Daltons.

The stabilized hydrogen peroxide generated from source of hydrogen peroxide is preferably hydrogen peroxide, sodium perborate e.g. sodium perborate tetrahydrate or sodium perborate decahydrate, sodium peroxide and urea peroxide, more preferably sodium perborate.

Accordingly, the present invention provides compositions for treatment of dry eye symptoms comprising

- i) a glycosaminoglycan, e.g. a hyaluronate, and

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- ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight based on the total weight of composition, e.g. generated from sodium perborate tetrahydrate in an amount of about 0.10 to about 0.15% by weight based on the total weight of composition.

The compositions of the present invention may further comprise a stabilizer. Preferred stabilizers include chelating agents having phosphonic acid or phosphonate groups. A preferred group of chelating agents are organophosphonates, particularly amino tri(lower alkylene phosphonic acids). A variety of such chelating agents are known and commercially available from Monsanto Company, St. Louis, under the trade name Dequest®. Examples of such compounds include e.g. diethylene triamine penta(methylene phosphonic acid); hexamethylene-diaminetetra (methylenephosphonic acid); ethylenediaminetetra(methylenephosphonic acid); and aminotrimethylene phosphonates. A particularly preferred chelating agent is diethylene triamine penta(methylene phosphonic acid), as known and commercially available under the trade name Dequest® 2060. Typically, a stabilizer is present in an amount from about 0.00001 to 0.5%, more preferably from about 0.0001 to 0.1% by weight based on the total weight of composition.

The compositions of the present invention may further comprise a tonicity enhancing agent. Suitable tonicity enhancing agents are, e.g.

- i) ionic compounds, such as alkali metal or alkaline earth metal halides, such as sodium chloride, sodium bromide, sodium iodide, lithium chloride, potassium chloride, potassium bromide, potassium iodide, calcium chloride e.g. as its 2-hydrate, magnesium chloride e.g. as its 6-hydrate, or boric acid, and/or
- ii) non-ionic compounds such as urea, or polyols e.g. glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

Preferably, a mixture of ionic and/or non-ionic tonicity enhancers is present. In a preferred embodiment, the compositions of the present invention comprise glycerol.

Conveniently, sufficient tonicity enhancing agent is added to impart to the ready-for-use ophthalmic composition a hypotonic osmolality of approximately from 150 to 400 mOsmol, preferred from 200 to 350 mOsmol, more preferred from 220 to 280 mOsmol. The tonicity agent is present in an amount which is sufficient to achieve an ophthalmically compatible

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composition having a hypotonic osmolality. Typically, the tonicity agent is present in an amount from about 0.01 to 10%.

For the adjustment of the pH, preferably to a slightly alkaline pH, a pharmaceutically acceptable buffer system may be added. Examples of buffer substances are acetate e.g. sodium acetate 3-hydrate, ascorbate, borate, e.g. sodium borate, hydrogen carbonate/carbonate, citrate e.g. tri-sodium citrate 2-hydrate, gluconate, lactate, phosphate e.g. Na_2HPO_4 , NaH_2PO_4 or KH_2PO_4 , propionate, tromethamine (tris-(hydroxymethyl)-amino-methane, TRIS) buffers and mixtures thereof. Borate buffer is preferred. The buffer substance added is typically of an amount to ensure and maintain a physiologically tolerable pH range. Typically, the buffer will be present in an amount from about 0.05 to 2.5%, preferably from about 0.1 to 1.5% by weight based on the total amount of composition. The pH range is generally in the range of from 6.5 to 9, preferably from 7.0 to 8.5 and more preferably from 7.5 to 8.0. The desired pH may be adjusted by addition of acid, e.g. HCl, or base, sodium hydroxide.

In another embodiment, the present invention provides for compositions further comprising an ophthalmic carrier. Such carriers are typically adapted for topical administration, and are for example, water, mixtures of water and water-miscible solvents, such as C_1 - to C_7 -alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethyl-cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinyl-pyrrolidone, or water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methyl-cellulose, alkali metal salts of carboxy-methylcellulose, hydroxymethylcellulose, hydroxyethyl-cellulose, methylhydroxypropyl-cellulose and hydroxypropylcellulose, preferably water.

Preferably, the compositions of the present invention are in form of a solution, e.g. artificial tears, e.g. having a viscosity of about 2 to about 60 mPas as determined using a capillary viscosimeter according to Eur. Ph., or in form of a gel, e.g. having a viscosity of about 200 to about 2000 mPas as determined using a rotary viscosimeter according to Eur. Ph.. Preferably, the compositions of the present invention are in form of a solution and are substantially free of organic polymers other than glycosaminoglycans.

It will be appreciated that although the excipients have been described above by reference to a particular function any particular excipient may have alternative or multiple functions, e.g.

boric acid may act as e.g. tonicity enhancer and/or buffer after addition of base e.g. sodium hydroxide.

In a particularly preferred embodiment, the ophthalmic composition of the present invention consists of

- i) a glycosaminoglycan, e.g. a hyaluronate, e.g. in an amount of 0.05 to 4% by weight,
- ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight, e.g. sodium perborate tetrahydrate in an amount of about 0.10 to about 0.15% by weight,
- iii) a stabilizer, e.g. in an amount of 0.0001 to 0.1% by weight,
- iv) one or more tonicity agents, e.g. in an amount of 0.01 to 10.0% by weight,
- v) a buffering agent, e.g. in an effective amount to maintain a pH of 6 to 8, and
- vi) water.

In another aspect, this invention provides a method of preserving an ophthalmic composition comprising a glycosaminoglycan, e.g. according to Eur. Ph. criteria A, which method comprises adding stabilized hydrogen peroxide generated from a source of hydrogen peroxide, e.g. sodium perborate, for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight to the ophthalmic composition, e.g. adding sodium perborate tetrahydrate in an amount of about 0.10 to about 0.15% by weight.

The ophthalmic compositions of the present invention may be prepared in conventional manner e.g. by mixing the excipients. The compositions of the present invention may be packaged in conventional manner. The compositions of the present invention may be stored in single or multiple unit dosage form, e.g. closed bottles, tubes or other containers made from glass, plastic such as e.g. polyethylene, polyethylene terephthalate, or polypropylene, or metal or combinations thereof. For example bottles may contain about 1 to 5 ml of the compositions of the present invention. The container may be fitted with a dropper to facilitate administration.

The compositions of the present invention may be formulated in conventional manner e.g. to be particularly adapted for topical ophthalmic use. In so far as the procedures for formulation

are not particularly described herein such formulation procedures may for example be known in the art, or analogous to those known in the art or to procedures described herein. Representative procedures are disclosed in for example, Remington's Pharmaceutical Sciences, 19th Ed., Mack Publ., Co., 1995, H. Sucker et al, Pharmazeutische Technologie, 2nd Edition, Thieme, 1991, R: H. Mueller et al, Pharmazeutische Technologie: Moderne Arzneimittelformen, 2nd Edition, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1998, L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, and Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, (Springer Verlag, 1971) as well as later editions, the contents of all of which are incorporated herein by reference.

The excipients used may e.g. be those known in the art e.g. in the Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Fiedler, H.P.; 1996; Editio Cantor Verlag Aulendorf (Germany), and Handbook of Pharmaceutical Excipients, Kibbe, A.H.; 2000, a joint publication of Pharmaceutical Press, London (UK), and American Pharmaceutical Association, Washington (US), references referred to above, or analogous to those known in the art or new excipients having analogous function to those described in the art or herein.

The compositions of the present invention are useful for the treatment of dry eye, or, more specifically, its symptoms, as indicated e.g. in standard animal trials and clinical trials. Additionally, these compositions can slow down the progress of the syndrome and reverse its effects including, in moderate to severe cases of dry eye, corneal staining, which is made evident by use of Rose Bengal or Fluorescein.

The ocular tolerance of the ophthalmic compositions of the present invention may be assessed with the test described infra:

The upper eyelid of the right eye is carefully pulled away from the eyeball and 50 microliter of the test substance is instilled (single dose instillation) on the outer superior part of the bulbar conjunctiva of three albino rabbits using a gauged automatic pipette. The contralateral eye is used as non treated control. The eyelid is gently closed for about one second. Before the instillation, for the 15 first minutes, 1, 2 and 7 days after the instillation, visual ocular examinations are carried out e.g. using a pen lamp. Anterior segment aspect is evaluated and scored according to Draize method. In addition discomfort is scored.

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A clinical trial may be effected to test the efficacy and tolerability of about 30 to 40 microlitre of compositions of the present invention administered once a day by instillation onto the ocular surface, e.g. to the inside lower lid, to groups of, e.g. 10 to 25, healthy volunteers, or patients suffering from allergic conjunctivitis. The trial lasts e.g. 8 days.

The subjects are examined to determine the effect against dry eye symptoms, e.g. fast onset of action and long duration of action and good tolerability.

The exact amount of composition of the present invention to be administered will naturally depend on a variety of factors, e.g. choice of salt, excipients, formulation properties, and severity of the condition. Typically, the dosage regimen is 10-50 microlitres of composition administered to the lower conjunctival sac of the affected eye, e.g. using a dropper.

The daily dose of composition of the present invention to be administered is from about 1 to 20 doses of 10-50 microliters of composition, typically three times a day. Frequency of dosing is variably dependent upon the severity of the syndrome. For severe cases dosing may occur 20 times per day. The frequency is reduced when signs of the disease state show improvement. At that time dosing may be as infrequent as one dose daily or once every two or three days.

Therefore, in a further aspect the present invention provides

- a) an ophthalmic composition as defined above for use in the treatment of dry eye symptoms, e.g. foreign body sensation, burning, and hyperemia,
- b) a method for treating dry eye symptoms or a condition treatable by glycosaminoglycan therapy comprising administering a composition of the present invention to the eye of a patient in need thereof, or
- c) the use of a composition of the present invention in the preparation of a medicament for the treatment of dry eye symptoms.

In particular, the present invention provides a method of treating dry eye symptoms comprising administering a composition comprising

- i) a glycosaminoglycan e.g. a hyaluronate, e.g. in an amount of 0.05 to 4% by weight, and
- ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of

about 0.02 to about 0.035% by weight, e.g. sodium perborate tetrahydrate in an amount of about 0.10 to about 0.15% by weight.

In particular, the present invention provides a method of treating dry eye symptoms comprising instilling a composition into the eye wherein said composition essentially consists of

- i) a glycosaminoglycan e.g. a hyaluronate, e.g. in an amount of 0.05 to 4% by weight,
- ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of 0.02 to 0.035% by weight, e.g. sodium perborate tetrahydrate in an amount of about 0.10 to about 0.15% by weight,
- iii) a stabilizer, e.g. in an amount of 0.0001 to 0.1% by weight,
- iv) one or more tonicity agents e.g. in an amount of 0.01 to 10.0% by weight,
- v) a buffering agent, e.g. in an effective amount to maintain a pH of 6 to 8, and
- vi) water.

All percentages referred to herein are % by weight based on the total amount of composition except where otherwise indicated.

Following is a description by way of example only of compositions of this invention.

Example 1 to 5:

amounts given in gram if not otherwise stated

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5
sodium hyaluronate tetrahydrate	0.2508	0.501	0.2499	0.5022	0.2506
Dequest®	0.015	0.015	0.015	0.015	0.015
sodium perborate	0.3502	0.3500	0.2501	0.2501	0.1755
sodium chloride	0.2250	0.28125	0.28125	0.28125	0.28125
potassium chloride	0.1875	0.1875	0.1875	0.1875	0.1875
calcium chloride 2-hydrate	0.12	0.12	0.12	0.12	0.12
magnesium chloride 6-hydrate	0.075	0.075	0.075	0.075	0.075
sodium acetate 3-hydrate	0.975	0.975	0.975	0.975	0.975
tri-sodium citrate 2-hydrate	0.425	0.425	0.425	0.425	0.425
boric acid	1.25	1.25	1.25	1.25	1.25
1N sodium hydroxide	-	-	0.4 ¹	0.4 ¹	1.3 ¹
water	in 250 ml	in 250 ml	in 250 ml	in 250 ml	in 250 ml

¹: amount in ml

Compositions of examples 1 to 5 meet criteria A requirements for efficacy of antimicrobial preservation of the Eur. Ph. (Eur. Ph. Supplement 2001, Section 5.1.3) for ophthalmic preparations.

Example 6 to 10:

amounts given in gram if not otherwise stated

	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10
sodium hyaluronate tetrahydrate	0.4992	0.2511	0.501	0.251	0.5003
Dequest®	0.015	0.015	0.015	0.015	0.015
sodium perborate	0.1750	0.1250	0.1251	0.07009	0.07009
sodium chloride	0.39375	0.9000	0.9000	0.9000	0.9000
potassium chloride	0.1875	0.1875	0.1875	0.1875	0.1875
calcium chloride 2-hydrate	0.12	0.12	0.12	0.12	0.12
magnesium chloride 6-hydrate	0.075	0.075	0.075	0.075	0.075
sodium acetate 3-hydrate	0.975	-	-	-	-
tri-sodium citrate 2-hydrate	0.425	-	-	-	-
boric acid	1.25	1.25	1.25	1.25	1.25
1N sodium hydroxide	0.7 ¹	1.5 ¹	1.7 ¹	1.9 ¹	1.7 ¹
water	in 250 ml	in 250 ml	in 250 ml	in 250 ml	in 250 ml

¹: amount in ml

Compositions of examples 6 to 10 meet the criteria A requirements for efficacy of anti-microbial preservation of the Eur. Ph. (Eur. Ph. Supplement 2001, Section 5.1.3) for ophthalmic preparations.

Example 11 to 14:

Compositions of examples 11 to 14 meet the criteria A requirements for efficacy of anti-microbial preservation of the Eur. Ph. (Eur. Ph. Supplement 2001, Section 5.1.3) for ophthalmic preparations.

amounts given in gram if not otherwise stated

	Ex. 11	Ex. 12	Ex. 13	Ex. 14
sodium hyaluronate tetrahydrate	0.10	0.20	0.10	0.10
Dequest	0.006	0.006	0.006	0.006
sodium perborate	0.14	0.14	0.12	0.1
potassium chloride	0.075	0.075	0.075	0.075
calcium chloride 2-hydrate	0.048	0.048	0.048	0.048
magnesium chloride 6-hydrate	0.03	0.03	0.03	0.03
sodium acetate 3-hydrate	0.39	0.39	0.39	0.39
tri-sodium citrate 2-hydrate	0.17	0.17	0.17	0.17
boric acid	0.5	0.5	0.5	0.5
glycerol	0.29	0.29	0.29	0.29
water	in 100 ml	in 100 ml	in 100 ml	in 100 ml

Example 15: Ocular Tolerance

Assessment of short-term ocular tolerance of ophthalmic formulations after a single dose administration of 50 microliters of compositions of examples 1 to 14 were instilled into the conjunctival sac of three female New-Zealand albino rabbits, weighing 3 to 5 kg. Neither discomfort, nor conjunctival redness, nor chemosis, nor discharge, nor corneal opacification, nor iris pathological findings were observed in any animal and at any time.

Claims

1. A composition for treatment of dry eye symptoms comprising
 - i) a glycosaminoglycan and
 - ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight.
2. A composition according to claim 1 further comprising a stabilizer.
3. A composition according to claim 1 or 2 further comprising a tonicity enhancer.
4. A composition according to any preceding claim wherein said composition is hypotonic.
5. A composition according to any preceding claim consisting essentially of
 - i) a glycosaminoglycan,
 - ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight,
 - iii) a stabilizer,
 - iv) one or more tonicity agents,
 - v) a buffering agent, and
 - vi) water.
6. A composition according to any preceding claim wherein the glycosaminoglycan is a hyaluronate.
7. A composition according to any preceding claim wherein the hydrogen peroxide source is sodium perborate tetrahydrate.
8. A composition according to claim 7 wherein the sodium perborate is present in an amount of about 0.10 to about 0.15% by weight.
9. A composition for treatment of dry eye symptoms which meet the criteria A requirements for efficacy of antimicrobial preservation of the European Pharmacopeia, Supplement 2001, Section 5.1.3, comprising a glycosaminoglycan.
10. A method of treating dry eye symptoms comprising administering a composition comprising
 - i) a glycosaminoglycan and
 - ii) stabilized hydrogen peroxide generated from a source of hydrogen peroxide for providing an effective trace amount of resultant hydrogen peroxide in an amount of about 0.02 to about 0.035% by weight.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08488

A. CLASSIFICATION OF SUBJECT MATTER

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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)

IPC 7 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 practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 19981 A (KARAGOEZIAN HAMPAR L) 13 April 2000 (2000-04-13) page 12; claims 16,19,20,40,43,44 page 17 -page 18; example 6 ---	1-10
A	US 4 973 580 A (MASCELLANI GIUSEPPE ET AL) 27 November 1990 (1990-11-27) example 6 ---	1-10
A	EP 0 710 483 A (ALFA WASSERMANN SPA) 8 May 1996 (1996-05-08) abstract; claim 1 --- -/--	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in 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 document 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.

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Date of the actual completion of the international search

8 October 2002

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

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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.
X	DEBBASCH C ET AL: "Cytotoxicity evaluation of three tear substitutes used in the treatment of dry eye syndromes!. Evaluation de la cytotoxicite de trois substituts lacrymaux utilises dans le traitement des syndromes secs." JOURNAL FRANCAIS D OPHTALMOLOGIE, (2000 NOV) 23 (9) 863-9., XP001028692 see discussion abstract -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08488

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7

Present claims 1-7 relate to compositions/methods defined by reference to a desirable characteristics or properties, namely: "a glycosaminoglycan", "hydrogen peroxide generated from a source of hydrogen peroxide providing an affective trace amount of resultant hydrogen peroxide....", " a stabilizer", "a tonicity enhancer", "a composition which meet the criteria A requirements for efficacy of antimicrobial preservation of the European Pharmacopeia..."

The claims cover all compositions/methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compositions/methods disclosed in the examples and in claims 8-10

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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