Abstract: The present invention relates to a sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl)-chitosan with a content of free thiol groups of from 80 to 280 umol/g polymer, for use in the treatment of a non-infectious corneal disorder, in particular dry eye diseases and persistent corneal epithelial defects, wherein said solution is applied intermittently, characterised by a scheme of treatment wherein the solution is applied to the eye for a period A of 5 days or more, then the application is paused for a period B of at least 2 and at most 180 days and then applied again for a period C of 1 day or more.
The present invention relates to the therapeutic use of a sterile ophthalmic solution comprising N-(N-acetylcysteinyl)-chitosan or a pharmaceutically acceptable salt thereof in a carrier solution for use in treatment and prevention of non-infectious corneal disorders, in particular dry eye diseases and corneal epithelial defects.

Background of the invention

Non-infectious corneal disorders can be related to a dysfunctional and/or instable tear film (e.g. lack of tear production, excessive tear production, increased tear evaporation) and/or corneal epithelial defects.

Dry eye diseases (DED) are highly prevalent corneal disorders. Approximately 40 million Americans are affected with some type of dry eye disease, a significant portion of which that are age 50 years and older have moderate-to-severe dry eye (Schaumberg, Sullivan et al., 2003, Prevalence of dry eye syndrome among US women, Am J Ophthalmol (136): 318-326; Schaumberg, Dana et al., 2009, Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies, Arch Ophthalmol (127): 763-768). Broadly, DED can be any symptoms associated with tear film instability and dysfunction (such as increased tear evaporation and/or reduced aqueous secretion). Various conditions affect the quality and stability of the tear film, which results in dry eye signs and symptoms and also negatively influence tear film functionality and frequently cause (temporary or chronic) dry eye diseases.

Among the indications that are referred to by the general term "dry eye disease" are: Keratoconjunctivitis sicca (KCS), age-related dry eye, Stevens-Johnson syndrome, Sjogren's syndrome, ocular cicatrical pemphigoid, corneal injury, ocular surface infection, Riley-Day syndrome, congenital alacrima, nutritional disorders or deficiencies (including vitamin deficiencies), pharmacologic side effects, glandular and tissue destruction, autoimmune and other immunodeficient disorders, and inability or limitation to blink (e.g. in comatose patients or patients with Parkinson's disease). Also included are dry eye symptoms caused by environmental exposure to airborne particulates, smoke, smog, and excessively dry air; as well as contact lens intolerance and eye stress caused by computer work or computer gaming. Persons with moderate to severe dry eye disease experience frequent or constant ocular discomfort.
Currently the management of DED encompasses both pharmacologic and non-pharmacologic treatments, including environmental management, avoidance of exacerbating factors, lid hygiene, tear supplementation (artificial tears), secretagogues (to increase the production of tears), punctual plugs, anti-inflammatory agents (cyclosporine, steroids), moisture chamber, and even salivary gland auto transplantation (Behrens, Doyle et al., 2006, Dysfunctional tear syndrome: a Delphi approach to treatment recommendations, Cornea (25): 900-907). Currently available options for treating DED are inadequate. Even tear supplementation is not an ideal treatment option as it requires the subject to repeat artificial tear installation very many times during the day.

Another subclass of non-infectious corneal disorders may be classified as corneal epithelial defects and damages. Mechanical corneal injuries are the most common ophthalmic injuries. They are often caused by the impact of external physical forces (e.g. branches, finger nails, make up applicators), which results in damage of small or large parts of the corneal surface. Foreign body-related abrasions are typically caused by pieces of airborne debris (such as pieces of metal, wood, glass, etc.) that have become embedded in the cornea. After removal of the foreign body defects in the corneal epithelium are left behind. Contact lens-related abrasions are defects in the corneal epithelium which are caused by contact lens overuse or the wearing of an improperly fitting, or improperly cleaned contact lens. Chemical corneal injuries are another reason for corneal trauma. Exposure to alkaline or acidic substances can cause extensive damage to the corneal surface.

Corneal epithelial damage also occurs as a result of intense exposure to ultraviolet light (photokeratitis) due to the failure to use adequate eye protection (e.g. snow blindness). Corneal wounds also occur in consequence of surgery, such as cataract surgery, corneal transplantation, glaucoma filtering surgery, and refractive eye surgery, such as photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK); or as corneal complications of intraocular surgery such as vitrectomy (Hammil, M. Bowes, 2011, Mechanical Injury. In Krachmer, Mannis et al. (editors): Cornea [3rd edition] Elsevier Inc.:1169-1185).

Recurrent corneal erosions are characterised by repeated episodes of corneal epithelial breakdown. They can be caused by corneal dystrophies such as epithelial basement membrane dystrophy or they can be the result of corneal minor trauma or abrasion (Steele, Chris, 1999, The role of therapeutic contact lenses in corneal wound healing, Optometry today (October 8): 36-40). The breakdown or loss of the epithelial layer leads to failures in the corneal surface integrity. Corneal wounds related to corneal erosions are thus mainly
epithelial damages. Epithelial defects that do not heal over a period of one or two weeks or
heal and break down repeatedly are for example non-healing corneal epithelial defects,
persistent corneal epithelial defects, slow-healing corneal epithelial defects, and neuropathic
(neurotrophic) epithelial defects.

Another epithelial defect with typical scattered, fine, punctate corneal epithelial loss or
damage is a so called superficial punctate keratitis (SPK). This corneal inflammation may be
a result of various causes such as viral conjunctivitis (most commonly adenovirus),
blepharitis, keratoconjunctivitis sicca, trachoma, chemical burns, ultraviolet (UV) light
exposure (e.g. welding arcs, sunlaps, snow glare), contact lens overwear, systemic drugs
(e.g. adenine arabinoside), topical drugs or preservation toxicity, and peripheral facial nerve
palsy (including Bell's palsy). Thus, the SPK may be caused by infections as well as
non-infectious reasons.

The treatment of non-infectious corneal epithelial defects and damages has three aims:
alleviation of the patient's symptoms via systemic and/or topical administration of pain
killers; prevention of infections (if deemed necessary) via topical instillation of antibiotics;
and protection of the corneal epithelium. Surgical procedures such as corneal transplantation
typically require additional medication for the postoperative phase; however eye drops for
the protection and lubrication of the corneal surface are part of the therapy.

Various polymers have been disclosed as possible aids in providing some benefit to
alleviating DED symptoms and the treatment of non-infectious corneal epithelial defects and
damages and in fact some artificial tears contain one or more polymers, including the
currently top 5 best selling over-the-counter (OTC) products for dry eye within the EU
(Celluvisc®, Systane®, Hylo-Comod®, Optive® and Artelac®). These polymers are
intended to protect ocular mucous membranes and provide lubrication for the ocular surface.
Examples include cellulose derivatives, hyaluronic acid, liquid polyols, polyvinyl alcohol,
povidone, carbopol and hydroxypropyl-guar. Polymers used in products to treat DED have
relatively short residence time on the ocular surface and require frequent instillation. In order
to increase ocular residence time, some formulations contain petroleum jelly or mineral oil;
however, due to significant blurring these highly viscous products can only be used in the
evening prior to sleep (Abelson et al., 2008, Tear Substitutes. In: Albert and Miller, eds.
Company, 287-292). All other tear substitutes have to be instilled repeatedly during the day.
Some potential improvements to these polymers have been disclosed. One potential improvement could be to use a polymer that has significant mucoadhesive properties in order to increase residence time of the formulation on the ocular surface without causing significant blurring. Chitosan, a polycationic polymer which is derived from the natural polymer chitin, is well known for its mucoadhesive properties. Ocular residence time of ophthalmic formulations containing chitosan can be increased not only due to its viscosity enhancing properties but also because of interactions of chitosan with negatively charged mucins on the ocular surface (Wadhwa, Paliwal et al., 2009, Chitosan and its role in ocular therapeutics, Mini Rev Med Chem (9): 1639-1647). In addition, chitosan has antimicrobial activity against various pathogenic microorganisms (Felt, Carrel et al., 2000, Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy, J Ocul Pharmacol Ther (16): 261-270; Dai, Tanaka et al., 2011, Chitosan preparations for wounds and burns: antimicrobial and wound-healing effects, Expert Rev Anti Infect Ther (9): 857-879).

It was found that eye drops containing 1.5% chitosan HCl had similar effects to recombinant bovine basic fibroblast growth factor eye drops on promoting the corneal epithelial healing process in a rabbit model. Eye drops applied three times a day containing 0.5% chitosan HCl displayed these promotive effects to a significantly lesser degree and performed only slightly better than the negative control (Yonghun Xu et al. 2009, Promotive Effects of CH-HCL Chitosan Solution on Epithelial Corneal Abrasion in Rabbits, Wuhan University Journal Medical Section 30(2): 173-176). However, the reports of the effects of chitosan on corneal wound healing are contradictory. A 1% solution of chitosan failed to improve corneal wound healing when applied three times a day for 3 weeks in a study using a rabbit model (Sail, Kreter et al., 1987, The effect of chitosan on corneal wound healing, Ann Ophthalmol (19): 31-33). Another research group reported that 0.5% solutions of chitosan stimulated corneal wound healing after 24h incubation of rabbit corneas in organ culture (Cui et al., 2014, Chitosan promoted the corneal epithelial wound healing via activation of ERK MAPK Pathway, Invest. Ophthalmol. Vis. Sci. 55(13):499).

WO 2011/127144 discloses the use of derivatized chitosans for a number of different wound healing applications, including the use of a chitosan-arginine polymer for the treatment of corneal wounds. In an alkali burn model of the rabbit cornea the 4 times daily application of a formulation containing a chitosan-arginine derivative for 9 days decreased inflammation and accelerated wound healing.

Thiolation of polymers has been disclosed to further increase their mucoadhesive properties. EP 1126881 B1 discloses a mucoadhesive polymer comprising at least one non-terminal
thiol group. The use of thiolated polysaccharides for preparing an implant for tissue augmentation is disclosed in WO 2008/077172, wherein said thiolated polymers are characterised by the formation of disulfide bonds which leads to a stabilisation of the polymeric network. The priority application of WO 2008/077172, AT A 2136/2006, discloses further application fields for thiolated polymers.


N-acetylcysteine (NAC) is a derivative of the thiol group bearing amino acid L-cysteine. NAC is a reducing agent with antioxidative activity. It is also well known for its ability to reduce mucus viscosity by reducing mucin disulfide bonds. Due to these mucolytic properties NAC is widely used to reduce mucus viscosity in broncho-pulmonary disorders with excessive mucus production. Topical ophthalmic formulations containing the mucolytic and antioxidant agent NAC are used for the treatment of corneal diseases such as meibomian gland dysfunction and DED (Lemp, 2008, Management of dry eye disease, Am J Manag Care (14): S88-101; Akyol-Salman, Azizi et al., 2010, Efficacy of topical N-acetylcysteine in the treatment of meibomian gland dysfunction, J Ocul Pharmacol Ther (26): 329-333). EP 0 551 848 B1 discloses an ophthalmic pharmaceutical composition for the treatment of DED containing NAC in a concentration between 3% and 5% (w/v) and polyvinylalcohol. It has been disclosed that thiolation of chitosan using NAC increases its ocular residence time on rabbit eyes when compared with non-thiolated chitosan (Dangl, Hornof et al., 2009, In vivo Evaluation of Ocular Residence Time of 124I-labelled Thiolated Chitosan in Rabbits Using MicroPET Technology, ARVO Meeting Abstracts (50): 3689).

It has been disclosed that N-(N-acetylcysteinyl-)chitosan HC1 has some beneficial effect on the ocular surface of the mouse eye in mouse dry eye models (Hongyok, Chae et al., 2009,

WO 2015/169728 discloses a sterile aqueous ophthalmic solution comprising about 0.05% to about 0.5% (w/w) of N-(N-acetylcysteinyl)-chitosan or a pharmaceutically acceptable salt thereof in a carrier solution, wherein the N-(N-acetylcysteinyl)-chitosan has a content of free thiol groups in an amount of from 80 μηιοι/g polymer to 280 μηιοι/g polymer, and the use of said solution for the treatment of DED. Beneficial effects of the chitosan-NAC solution on corneal wound healing has been identified previously (WO 2017/072236). As standard for aqueous ocular lubricants, the aqueous ophthalmic solution is applied once or twice a day.

For patients with non-infectious corneal disorders, especially those wherein a dysfunctional and/or instable tear film and/or the persistence of corneal epithelial defects are related to an underlying chronic disease or condition, the regular and repeated application of lubricants into the eye(s) is cumbersome. It is an object of the present invention to provide a pharmaceutical preparation suitable for the prevention or treatment of non-infectious corneal disorders, in particular dry eye diseases or persistent corneal epithelial defects with manageable and improved therapeutic use.

Summary of the invention

The present invention provides a sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl)-chitosan or a pharmaceutically acceptable salt thereof in a carrier solution, wherein the N-(N-acetylcystleinyl)-chitosan has a content of free thiol groups in an amount of from 80 μηιοι/g polymer to 280 μηιοι/g polymer, for the specific use in the prevention or treatment of a non-infectious corneal disorder, in particular a dry eye disease or a persistent
corneal epithelial defect, wherein said solution is applied intermittently with a period A during which period A said solution is applied and wherein the length of period A is 5 or more subsequent days, and with a period B following said period A during which period B application of said solution is ceased, and wherein the length of period B is at least 2 subsequent days and at most 180 subsequent days and with a period C following said period B during which period C said solution is applied and wherein the length of period C is 1 or more day(s).

Preferred embodiments of the present invention are listed in the dependent claims.

In another aspect, the present invention provides a method of treatment or prevention of a subject with a non-infectious corneal disorder, in particular a dry eye disease or a persistent corneal epithelial defect, wherein a sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl-)chitosan as defined above, is applied intermittently with a period A during which period A said solution is applied and wherein the length of period A is 5 or more subsequent days, and with a period B following said period A during which period B application of said solution is ceased, and wherein the length of period B is at least 2 subsequent days and in particular at most 180 subsequent days and with a period C following said period B during which period C said solution is applied and wherein the length of period C is 1 or more day(s).

Detailed description of the invention

In the following, the term "chitosan-NAC" stands for both N-(N-acetylcysteinyl-)chitosan and pharmaceutically acceptable salts thereof.

Surprisingly, a sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl-)chitosan showed a long-lasting positive effect even after interruption of the treatment. For example, the improvement of dry eye signs (such as tear film break up time) and/or dry eye symptoms (such as ocular discomfort) achieved during the treatment phase was at least maintained during the treatment pause. This finding is basis for the intermittent administration regime according to the present invention. Without wishing to be bound by any theory, the long-lasting effect may be due to the mucoadhesive properties, the extent of which is surprisingly high and consequently long ocular residence time for the sterile ophthalmic chitosan-NAC solution and its ability to form a durable protective coating on the ocular surface and to stabilize the tear film. Advantages of the intermittent administration regime according to the invention are numerous and may include for example increased
patient compliance, reduced side effect (e.g. reduced risk of infection by improper application of the solution), avoidance of tolerance effect, and so on.

The intermittent administration regime according to the present invention includes two types of time periods, i.e. one wherein the chitosan-NAC solution is applied (period A and C) and another one, wherein the chitosan-NAC solution is not applied, i.e. wherein the application is paused (period B, optionally period B’ as discussed below). Period A refers to a time period, wherein the use according to the present invention is initiated. Period B refers to a time period, wherein no solution is applied and the first period B directly follows period A. Subsequently, period C, a further period of applying the chitosan-NAC solution follows. Any period of the use or method according to the invention has a length, said length is typically expressed in days or weeks. When it is indicated that a period is having x day(s), this is synonym to the length of said period being x day(s). A reference to x days is to be understood as x subsequent days.

As it was found that the beneficial effect of said ophthalmic solution lasts surprisingly long after only a few days of application of the chitosan-NAC solution (s. reference examples), the administration regime according to the invention previews that the period A has at least 5 days and the period B has 2 to 180 days.

In one embodiment, the length of the period B is dependent on the length of the initial period A and this dependence may expressed according to the following equation I:

\[ B = f \times A \] \quad \text{Equation (I)}

The ratio of both lengths depends on the factor f, which was identified to be within the range of 0.2 to 36. Factor f may be any real number in the specified range, and accordingly also the result of the multiplication may be a non-natural number. However, A and B should be natural numbers (positive integers) to indicate a reasonable time period A or B in full days. Thus, the length of period B in days is obtained by multiplying A with f and in case the result is no integer, it is rounded up to the next natural number. This is also indicated by the ceiling function in equation I. Also in this embodiment, the provision applies that the length of period B is at least 2 and that period B does not extend 180 days.

According to a further embodiment, the length of period B is in the range of 5 to 90 days.
In some embodiments, \( f \) is at least 1, thus the period \( B \) is at least as long as period \( A \). This is based on surprising findings that the beneficial effect of said ophthalmic solution lasts surprisingly longer than the actual initial treatment (cf. Examples).

Furthermore, for preferred embodiments, the factor \( f \) may further depend on the length of period \( A \) according to the following provisions:
- if length of period \( A \) is in the range of from 5 to 10 days, \( f \) is in the range of from 0.4 to 36, preferably 1 to 18, more preferably 1 to 9, i.e. length of period \( B \) is in the range of from 2 to 180 days, preferably 5 to 180 days, more preferably 5 to 90 days;
- if length of period \( A \) is in the range of from 11 to 14 days, \( f \) is in the range of from 0.3 to 17, preferably 0.4 to 8, more preferably 0.4 to 4, i.e. length of period \( B \) is in the range of from 4 to 180 days, preferably 5 to 112 days, more preferably 5 to 56 days;
- if length of period \( A \) is in the range of from 15 to 29 days, \( f \) is in the range of from 0.3 to 12, preferably 0.3 to 6, more preferably 0.3 to 3, i.e. length of period \( B \) is in the range of from 5 to 180 days, preferably 5 to 174, more preferably 5 to 87 days;
- if length of period \( A \) is in the range of from 30 to 42 days, \( f \) is in the range of from 0.2 to 6, preferably 0.2 to 3, more preferably 0.2 to 1.5, i.e. length of period \( B \) is in the range of from 6 to 180 days, preferably 6 to 126 days, more preferably 6 to 63 days.

It will be appreciated that with a longer period \( A \), preferred values of \( f \) are found within the lower range of 0.2 to 36; in contrast, for a shorter period \( A \), the preferred values for the length of period \( B \) are shifted towards higher ranges.

In the following table, details of the treatment regime according to the invention are visualized and preferred embodiments or examples indicated.

Table 1
<table>
<thead>
<tr>
<th>Values/Ranges of values</th>
<th>Length of period A in days</th>
<th>period A in weeks</th>
<th>Factor f</th>
<th>Length of period B in days</th>
<th>period B in weeks</th>
<th>Length of period C in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to the invention</td>
<td>≥ 5</td>
<td>≥ 0.7</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred length of A and B</td>
<td>5 to 42</td>
<td>0.7 to 6</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred length of A and B</td>
<td>5 to 30</td>
<td>0.7 to 4.3</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred length of A and B</td>
<td>7 to 21</td>
<td>1 to 3</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred value for factor f</td>
<td>≥ 5</td>
<td>≥ 0.7</td>
<td>1 to 18</td>
<td>5 to 180</td>
<td>0.7 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred combination of length of A and factor f</td>
<td>5 to 10</td>
<td>0.7 to 1.4</td>
<td>0.4 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred combination of length of A and factor f</td>
<td>5 to 10</td>
<td>0.7 to 1.4</td>
<td>1 to 18</td>
<td>5 to 180</td>
<td>0.3 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred combination of length of A and factor f</td>
<td>11 to 14</td>
<td>1.6 to 2</td>
<td>0.3 to 17</td>
<td>4 to 180</td>
<td>0.6 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred combination of length of A and factor f</td>
<td>11 to 14</td>
<td>1.6 to 2</td>
<td>0.4 to 8</td>
<td>5 to 112</td>
<td>0.7 to 16.0</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred combination of length of A and factor f</td>
<td>15 to 29</td>
<td>2.1 to 4.1</td>
<td>0.3 to 12</td>
<td>5 to 180</td>
<td>0.7 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred combination of length of A and factor f</td>
<td>15 to 29</td>
<td>2.1 to 4.1</td>
<td>0.3 to 6</td>
<td>5 to 174</td>
<td>0.7 to 24.9</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred combination of length of A and factor f</td>
<td>30 to 42</td>
<td>4.3 to 6.0</td>
<td>0.2 to 6</td>
<td>6 to 180</td>
<td>0.9 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>More preferred combination of length of A and factor f</td>
<td>30 to 42</td>
<td>4.3 to 6.0</td>
<td>0.2 to 3</td>
<td>6 to 126</td>
<td>0.9 to 25.7</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Preferred length of C</td>
<td>≥ 5</td>
<td>≥ 0.7</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>1 to 42</td>
</tr>
<tr>
<td>Preferred length of C</td>
<td>≥ 5</td>
<td>≥ 0.7</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>1 to 30</td>
</tr>
<tr>
<td>Values/Ranges of values</td>
<td>Length of period A in days</td>
<td>period A in weeks</td>
<td>Factor f</td>
<td>Length of period B in days</td>
<td>period B in weeks</td>
<td>Length of period C in days</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>----------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Preferred length of C</td>
<td>≥ 5</td>
<td>≥ 0.7</td>
<td>0.2 to 36</td>
<td>2 to 180</td>
<td>0.3 to 25.7</td>
<td>1 to 7</td>
</tr>
<tr>
<td>Exemplary embodiment 1</td>
<td>5</td>
<td>0.7</td>
<td>1</td>
<td>5</td>
<td>0.7</td>
<td>1, 2, 5, 7, or 10</td>
</tr>
<tr>
<td>Exemplary embodiment 2</td>
<td>7</td>
<td>1.0</td>
<td>0.4</td>
<td>3</td>
<td>0.4</td>
<td>1, 2, 5, 7 or 10</td>
</tr>
<tr>
<td>Exemplary embodiment 3</td>
<td>10</td>
<td>1.4</td>
<td>12</td>
<td>120</td>
<td>17.1</td>
<td>5, 7 or 10</td>
</tr>
<tr>
<td>Exemplary embodiment 4</td>
<td>7 to 42</td>
<td>1 to 6</td>
<td>2</td>
<td>14 to 84</td>
<td>2 to 12</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Exemplary embodiment 5</td>
<td>30</td>
<td>4.3</td>
<td>0.92 to 1.02</td>
<td>28 to 31</td>
<td>4 to 4.4</td>
<td>1</td>
</tr>
<tr>
<td>Exemplary embodiment 6</td>
<td>28</td>
<td>4</td>
<td>0.75</td>
<td>21</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Exemplary embodiment 7</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>21</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Exemplary embodiment 8</td>
<td>5</td>
<td>0.7</td>
<td>0.4 to 0.8</td>
<td>2 to 4</td>
<td>0.29 - 0.57</td>
<td>1</td>
</tr>
<tr>
<td>Exemplary embodiment 9</td>
<td>5</td>
<td>0.7</td>
<td>0.6</td>
<td>3</td>
<td>0.42</td>
<td>1</td>
</tr>
</tbody>
</table>

After intermittence period B, use of the ophthalmic solution is continued during a further period of application (period C). The application during period C may be considered as maintenance dosage to refresh the therapeutic effect established in period A.

Regarding the length of period C, it should be noted that period C may be a short period, i.e. a period with few applications or even one application of the chitosan-NAC solution is sufficient. Thus, the length of period C in day(s) is 1 or more. Preferably, the length of period C is in the range of 1 to 42 days, more preferably the length of period C is in the range of 1 to 30 days or in the range of 1 to 21 days. Even more preferably, the length of period C is in the range of 1 to 10 days or 1 to 5 days. Exemplarily period C is 1, 2, 5, 7 or 10 days. In some embodiments, the length of period C is substantially shorter than that of period A.

In order to provide a sustainable application regime for non-infectious corneal disorders, after the period C optionally further periods of non-application and application may follow,
i.e., a further period B’ following said period C during which period B’ application of said solution again is ceased and a further period C following period B’ during which period C said solution is applied. Thus, the present invention defines a sequence of two periods, which sequence comprises a period B’, during which period B’ application of said solution is ceased, and a period C, during which period C said solution is applied.

Thus, in a preferred embodiment, the intermittent application for use according to the invention includes a sequence following period C, wherein the sequence is comprising a period B’, during which period B’ application of said solution is again ceased, and a period C, during which period C said solution is applied. Preferably, this sequence (comprising a period B’ and a period C) is repeated at least once.

The sequence of period B’ (no applying) and period C (applying) may be repeated for continued treatment after the initial period A. Preferably, the period C is followed by a further treatment pause of period B’ and a further period C of application, and so on. Consequently, the compound is provided for a specific use of periodically repeated phases of application and pausing the use of the chitosan-NAC solution. Each period B or B’ and any following periods, wherein said ophthalmic solution is not applied, may be considered as structured/strategic treatment interruption or drug/medicament vacation/holiday.

In one embodiment, period B’ is as long as period B or longer. Preferably, any interval of non-application (period B and period(s) B’) has the same length. Similarly, preferably period(s) C is/are as long as period C or longer, wherein the length of the period(s) is at least one day.

For example after an initial period A, e.g. of 5 to 30 days, the use according to the invention might be continued by applying the solution once in a month, i.e. monthly. Thus, in these cases period B, and optional periods B’, is/are 27 to 30 and each period C/C is one day.

Such an application scheme may be considered convenient as the last day of period A (for example 15th of May), may form a basis for easy calculation of any further application. The next application is due on the day in the relevant subsequent month, which has the same number as the day on which the period A was stopped (e.g. 15th of June). If the relevant subsequent month has no day with the same number, the period B or B’ ends before the last day of that month. In consequence, the length of the period B or B’ depends on the length of the relevant month and ranges between 27 and 30 days (s. exemplary embodiment 5 in Table 1).
In another example, a 28-day rhythm might underlie the sequences of period B and C. This is for example the case, wherein after an initial treatment period A, the application is ceased for 3 weeks and then the application is resumed for 1 week, followed again by 3 weeks of non-application and one week of application, and so on. embodiments with a 28-day rhythm might be preferred in subjects familiar with a 28-day rhythm, e.g. women taking oral contraceptives.

In another example, a shorter rhythm might underlie the sequences of periods B/B' and C/C. This is shown in the exemplary embodiment 8 or 9 according to table 1. In these cases, after an initial treatment period A of 5 days, the application is repeated every third to fifth day, i.e. ceased for period B of 2 to 4 days and then the application period C is one day, and so on. A sustained therapeutic effect could be obtained for example with a regime, wherein the solution was applied every third to fourth day, while the application effort was kept at a low and convenient level as shown in Example 6 below.

For embodiments including multiple sequences of periods B’ and C’, it is preferred that said periods are repeated to obtain a longer overall treatment period (first day of period A to last day of last period C). The overall treatment period may be several months, e.g. sequences of periods B’ and C’ are repeated to obtain an overall treatment period of about 4, 6, 9 or 12 months.

The following information on administering or applying the chitosan-NAC solution may apply for the period A as well as any following period C or period(s) C' of applying the ophthalmic solution for use according to the invention. If treatment or prevention is intended for both eyes, any formulation as used herein should be understood as "per eye". The application of the chitosan-NAC in period A or C includes applying the solution as eye drops at least once daily, e.g. once or twice. In a preferred embodiment during period A, during period C and/or during optional period(s) C', the ophthalmic solution for use according to the present invention is applied once daily.

The wording "once daily" for application of the composition for use according the invention is meant to be understood as one application per day, i.e. one time within 24 hours. The wording has a meaning equivalent to once per day, every day, the Latin expression "quaque die" and abbreviations q.d. (or qd) and o.d. (or od).

Moreover, it was found that the application of chitosan-NAC solution is especially beneficial if said ophthalmic solution is applied prior to sleep (WO 2017/072235).
Thus, in a more preferred embodiment, during period A, during period C and/or during optional period(s) C, the ophthalmic solution for use according to the present invention is applied prior to sleep.

The wording "prior to sleep" refers to an application before going to sleep. "Sleep" refers to a periodic physiological loss of consciousness. By "periodic" it is understood to mean a substantially uniform repeating pattern. For example, an adult may sleep approximately 8 hours per day. The application prior to sleep covers also the application at a time point prior to a period of night's rest or state of calm independent of loss of consciousness. With other words, the application is preferred before going to bed with the intention to sleep. Synonym terms could be "omne nocte on", a Latin term for "every night", or "hora somni", Latin for "at the hour of sleep". Thus, the application is preferred at bedtime. In context of the present invention it is preferred that the medication is applied immediately before going to sleep. It is preferred that the wording used for instructing the application refers to going "to sleep" rather than going "to bed" as activities like reading or watching TV or the like should not be encouraged between application and the effective sleep. Preferably, the ophthalmic solution for use according to the invention is applied 1 hour before to immediately prior to sleep, more preferably immediately prior to sleep.

In a further preferred embodiment, the ophthalmic solution for use according to the present invention is applied once per day prior to sleep.

The present invention is suitable for treatment and prevention of a non-infectious corneal disorder. It is expected that treatment and prevention of non-infectious corneal disorders profit from the long-lasting tear film stabilisation and protective coating on the ocular surface of the use according to the present invention. The use according to the present invention is expected to be especially beneficial for prevention and treatment of non-infectious corneal disorders related to a dysfunctional tear film (e.g. lack of tear production, excessive tear production, increased tear evaporation, decreased tear film stability) and persistent corneal epithelial defects and damages. Thus, in a preferred embodiment the non-infectious corneal disorder is a persistent corneal epithelial defect or a dry eye disease. It should be noted that corneal wounds are frequently accompanied by dry eye symptoms and vice versa.

In a preferred embodiment, the chitosan-NAC solution is used for the treatment or prevention of a dry eye disease, wherein this term includes dry eye syndrome as well as dry
eye signs and/or symptoms. Broadly, "dry eye syndrome" or "dry eye disease" as pertaining to the present invention can be any syndrome associated with tear film instability and/or dysfunction (such as increased tear evaporation and/or reduced aqueous secretion). However, it should be appreciated that the present invention, i.e. the ophthalmic solution for use in treatment or prevention, is especially beneficial for those, wherein the dry eye disease is moderate to severe and/or chronic and who experience frequent or constant ocular discomfort. An established classification scheme describes dry eye severity level 1 to 4 (The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). (No authors listed). The Ocular Surface 2007;5(2):75-92). Accordingly, in a preferred embodiment for use according to the invention, the dry eye disease has a dry eye severity level of 2 to 4, preferably 3 to 4. In one embodiment of the present invention the dry eye disease is chronic. As used herein, the term "chronic dry eye disease" refers to a condition, wherein the dry eye disease is persistent or (re)occurring regularly, i.e. not temporary.

In another embodiment, the chitosan-NAC solution is used for the treatment or prevention, in particular the treatment, of a corneal epithelial defect. Especially, the invention is useful in context of a persistent corneal epithelial defect. A persistent corneal epithelial defect occurs when corneal re-epithelialization does not take place within the normal two-week time frame or the corneal epithelium heals and breaks down repeatedly (e.g. recurrent corneal erosions).

Particularly, the present invention is suitable for use in treatment and prevention of a non-infectious disorder, wherein the non-infectious corneal disorder is associated with a diagnose selected out of the group consisting of age related dry eye; congenital alacrima; Riley Day syndrome (familial dysautonomia); sarcoidosis, lymphoma, AIDS, Graft vs host disease (result in lacrimal gland deficiencies); chemical and thermal burns, erythema multiforme, cicatricial pemphigoid and mucous membrane pemphigoid, trachoma (lead to lacrimal gland duct obstruction); damage of corneal, conjunctival and/or lid tissue, of lacrimal glands, of lacrimal ducts; menopause; autoimmune diseases which affect the ocular surface: such as Sjogren Syndrome, rheumatoid arthritis, systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis, mixed connective tissue disease; thyroid associated diseases (such as Graves' eye disease; Hashimoto thyroiditis); Diabetes; neurotrophic keratitis; loss of lacrimal secretomotor function, which might be consequence of a central nerve damage; side effect of systemic drugs such as antihistamines, beta blockers, antispasmodics, diuretics, antidepressants, sleeping pills, birth control pills, isotretinoin-type drugs, opiates, hormone replacement therapy; meibomian gland dysfunction; chronic blepharitis; Parkinson Disease (low blink rate); disorders of lid
aperture and lid/globe congruity: such as proptosis, high myopia, endocrine exophthalmos; may be caused by problems of lid congruity after plastic surgery, incomplete lid closure (lagophthalmos); ocular surface disorders caused by vitamin A deficiency or topical drugs (e.g. chronic glaucoma treatment) and preservatives; chronic contact lens wear; chronic allergic conjunctivitis; non-healing corneal epithelial defects, persistent corneal epithelial defects, slow-healing corneal epithelial defects, and neuropathic (neurotrophic) epithelial defects; corneal transplantation; limbal stem cell deficiency; laser eye surgery (especially laser assisted vision correction procedures such as photorefractive keratectomy (PRK), laser-assisted sub-epithelial keratectomy (LASEK) and laser-assisted in situ keratomileusis (LASIK)); Stevens-Johnson-Syndrome; recurrent corneal erosions; superficial punctate keratitis (SPK); glaucoma; surgical lesions.

Preferably, the N-(N-acetylcysteinyl-)chitosan or pharmaceutically acceptable salt thereof in said solution for use according to the present invention has a content of free thiol groups in an amount of from 105 μηοil/g polymer to 250 μηοil/g polymer, preferably of from 110 μηοil/g polymer to 250 μηοil/g polymer, most preferably of from preferably 140 to 250 μηοil/g polymer.

Preferably, in the sterile aqueous ophthalmic solution the concentration of the N-(N-acetylcysteinyl-)chitosan or said pharmaceutically acceptable salt thereof in said solution is from 0.05 to 0.3% (w/w), preferably from 0.05 to 0.2% (w/w), more preferably 0.08 - 0.16% (w/w).

In a further preferred embodiment, said pharmaceutically acceptable salt is selected from the group consisting of salts of organic acids such as acetic, citric, formic and tartaric acid, and salts of mineral acids such as HCl and H2SO4.

In view of further preferred embodiments related to the composition of the sterile aqueous ophthalmic solution, reference is made to WO 2015/169728.

EXAMPLES

Example 1: case study in a patient with dry eye syndrome (reference example)
A female patient of 77 years diagnosed with dry eye syndrome (no superficial punctate keratitis; SPK) presented with tearing eyes as well as tearfilm break up time of 3 seconds (right eye), and 5 seconds (left eye). Use of a sodium hyaluronate based lubricant (Hylo-Gel) as needed represented the established therapeutic regime.
At day 0 once daily application of an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 μηοι free thiol groups / g polymer, polyethylene glycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer was started. At day 5, the symptoms were improved. The eye examination revealed no SPK and tear film break up time for both eyes was 10 sec. Medication with Hylo-Gel as needed and the chitosan-NAC solution was continued.

At day 14, the improvement was observed to continue: no SPK, tear film break up time for both eyes was 12 sec. The treatment with the chitosan-NAC solution was paused. The use of Hylo-Gel as needed was continued.

An eye examination 4 weeks after treatment start, wherein the chitosan-NAC solution was not applied for 2 weeks, revealed still no SPK and the patient reported that the improvement of symptoms was maintained. An eye examination 5 weeks after treatment start, wherein the chitosan-NAC solution was not applied for 3 weeks, revealed similar findings.

Example 2: case study in a patient with dry eye syndrome and SPK (reference example)
A female patient (48 years old) presented with severe dry eye symptoms. The examination revealed superficial punctate keratitis (lower third of the cornea) as well as tear film break up time of 3 sec (right eye) and 10 sec (left eye). The patient already used artificial tears (HyloComod, Systane balance), when needed (at least 6 times a day).

At day 0 (baseline) treatment with an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 μηοι free thiol groups / g polymer, polyethylene glycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer was started once daily.

An eye examination was performed at day 7, and a pronounced improvement in dry eye symptoms was observed; no superficial punctate keratitis (SPK); no change in tear film break up time. The treatment with the chitosan-NAC solution was subsequently stopped after 10 days of once daily application.

During the subsequent period of non-treatment improvement continued. At day 14, an eye examination revealed significant improvement of ocular symptoms and reduced frequency of artificial tears application (3 to 4 times daily). Tear film break up time was >10 sec in the
right eye and >12 sec in the left eye. No fluorescence staining and no SPK was detected. Symptoms like redness and blurring had completely ceased.

Example 3: case study in a patient with dry eye syndrome
A female patient of 70 years diagnosed with dry eye syndrome presented with burning eyes, blurred vision and foreign body sensation. The examination revealed superficial punctate keratitis (SPK) in the lower third of the cornea and a tearfilm break up time of 5 seconds (both eyes). Schirmer's test results were 5 mm (right eye) and 10 mm (left eye). Use of a sodium hyaluronate based lubricant (Hyloparin) and a vitamin A eye ointment as needed represented the established therapeutic regime.

At the day of examination once daily application of an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 µηοï free thiol groups / g polymer, polyethyenglycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer was started. Medication with Hyloparin and the ointment as needed was continued.

After five days of treatment, dry eye symptoms were improved. The eye examination revealed an improvement in SPK. While the tearfilm break up time for both eyes remained unchanged, Schirmer's test results were 15 mm (both eyes).

The treatment with the chitosan-NAC solution was paused for 30 days.

An eye examination after the treatment pause revealed uniform SPK and a tearfilm break up time of 3 seconds in both eyes. Dry eye symptoms were burning and foreign body sensation. Treatment with the chitosan-NAC solution (once daily) was resumed. Medication with Hyloparin and a vitamin A eye ointment as needed was continued. After 12 days of treatment, an improvement in SPK was noted and only the lower third of the cornea was affected in both eyes. Dry eye symptoms remained unchanged.

After a further 7 days of treatment with the chitosan-NAC solution SPK was further improved. The tearfilm break up time for both eyes was 3 seconds, Schirmer's test results were 15 mm (both eyes). Dry eye symptoms remained unchanged.

Example 4: case study in a patient with dry eye syndrome and Morbus Crohn
A female patient of 53 years diagnosed with dry eye syndrome and Morbus Crohn presented with itching eyes and foreign body sensation. The examination revealed superficial punctate
keratitis (SPK) in the lower third of the cornea of the left eye and a tearfilm break up time of one second (both eyes).

At day 0 once daily application of an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 µηοï free thiol groups / g polymer, polyethylenglycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer was started. After 5 days of treatment, the application was paused for 7 days.

After further treatment for 22 days, dry eye symptoms were worsening. The eye examination revealed a worsened SPK. Treatment was continued for another 38 days, after which dry eye symptoms and SPK were improved.

Example 5: case study in male patient with dry eyes
A male patient suffered from severe dry eye. He applied an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 µηοï free thiol groups / g polymer, polyethylenglycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer twice daily for a time period of 6 weeks and noted an improvement in dry eye symptoms. Application was paused and resumed as needed when the patient noted a worsening of the symptoms during a time period of about 5 months.

Example 6: case study in female patient with dry eye symptoms
A female patient with dry eye symptoms applied an aqueous ophthalmic solution with a pH of 6.3 comprising 0.1% w/w chitosan-NAC with a degree of modification of 210 µηοï free thiol groups / g polymer, polyethylenglycol 40, hydroxypropyl methylcellulose and mannitol in a boric acid buffer once daily for five consecutive days (period A of 5 days) and noted improvement in dry eye symptoms. Over a time period of about 9 months the patient continued to apply the chitosan-NAC solution once daily every third or every fourth day to maintain the improvement of dry eye symptoms (periods B/B' of 2 to 3 days; period C/C' of 1 day).
Claims:

1. A sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl-)chitosan or a pharmaceutically acceptable salt thereof in a carrier solution, wherein the N-(N-acetylcysteinyl-)chitosan has a content of free thiol groups in an amount of from 80 µmol/g polymer to 280 µmol/g polymer, for the specific use in the prevention or treatment of a non-infectious corneal disorder wherein said solution is applied intermittently with a period A during which period said solution is applied, and wherein the length of period A is 5 or more subsequent days, and with a period B following said period A during which period B application of said solution is ceased, and wherein the length of period B is at least 2 subsequent days and at most 180 subsequent days, and with a period C following said period B during which period C said solution is applied, and wherein the length of period C is 1 or more subsequent day(s).

2. Ophthalmic solution for use according to claim 1, wherein the length of period B depends on the length period A according to the following provisions
   - if the length period A is in the range of from 5 to 10 days, the length of period B is in the range of from 2 to 180 days, preferably 5 to 180 days, more preferably 5 to 90 days;
   - if the length period A is in the range of from 11 to 14 days, the length of period B is in the range of from 4 to 180 days, preferably 5 to 112 days, more preferably 5 to 56 days;
   - if the length period A is in the range of from 15 to 29 days, the length of period B is in the range of from 5 to 180 days, preferably 5 to 174, more preferably 5 to 87 days;
   - if the length period A is in the range of from 30 to 42 days, the length of period B is in the range of from 6 to 180 days, preferably 6 to 126 days, more preferably 6 to 63 days.

3. Ophthalmic solution for use according to claim 1 or 2, wherein the length of period A is in the range from 5 to 42 days, preferably 5 to 30 days, more preferably 7 to 21 days.

4. Ophthalmic solution for use according to any of the preceding claims, wherein the length of period C is 1 to 42 days, preferably 1 to 30 days, more preferably 1 to 21 days.
5. Ophthalmic solution for use according to any of the preceding claims comprising a sequence following said period C, wherein said sequence comprises a further period B’ during which period B’ application of said solution again is ceased and a further period C during which period C said solution is applied.

6. Ophthalmic solution for use according to claim 5, wherein the sequence comprising period B’ and period C is repeated at least once.

7. Ophthalmic solution for use according to claim 6, wherein the length of period B and further periods B’ is 2 to 4 days and the length of period C and further periods C is 1 day, preferably the length of period B and further periods B’ is 2 to 3 days.

8. Ophthalmic solution for use according to any of the preceding claims, wherein during said period A and/or said period C said solution is applied once daily.

9. Ophthalmic solution for use according to any of the preceding claims, wherein during said period A and/or said period C said solution is applied prior to sleep.

10. Ophthalmic solution for use according to any of the preceding claims, wherein the non-infectious corneal disorder is a dry eye disease, preferably a dry eye disease of severity level 2 to 4.

11. Ophthalmic solution for use according to any of the preceding claims, wherein the non-infectious corneal disorder is a corneal epithelial defect, preferably a persistent corneal epithelial defect.

12. Ophthalmic solution for use according to any of the preceding claims, wherein the non-infectious corneal disorder is associated with a diagnose selected out of the group consisting of age related dry eye; congenital alacrima; Riley Day syndrome (familial dysautonomia); sarcoidosis, lymphoma, AIDS, Graft vs host disease (result in lacrimal gland deficiencies); chemical and thermal burns, erythema multiforme, cicatricial pemphigoid and mucous membrane pemphigoid, trachoma (lead to lacrimal gland duct obstruction); damage of corneal, conjunctival and/or lid tissue, of lacrimal glands, of lacrimal ducts; menopause; autoimmune diseases which affect the ocular surface: such as Sjogren Syndrome, rheumatoid arthritis, systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis,
primary biliary sclerosis, mixed connective tissue disease; thyroid associated diseases (such as Graves’ eye disease; Hashimoto thyroiditis); diabetes; neurotrophic keratitis; loss of lacrimal secretomotor function, which might be consequence of a central nerve damage; side effect of systemic drugs such as antihistamines, beta blockers, antispasmodics, diuretics, antidepressants, sleeping pills, birth control pills, isotretinoin-type drugs, opiates, hormone replacement therapy; meibomian gland dysfunction; chronic blepharitis; Parkinson disease (low blink rate); disorders of lid aperture and lid/globe congruity: such as proptosis, high myopia, endocrine exophthalmos; may be caused by problems of lid congruity after plastic surgery, incomplete lid closure (lagophthalmos); ocular surface disorders caused by vitamin A deficiency or topical drugs (e.g. chronic glaucoma treatment) and preservatives; chronic contact lens wear; chronic allergic conjunctivitis; non-healing corneal epithelial defects, persistent corneal epithelial defects, slow-healing corneal epithelial defects, and neuropathic (neurotrophic) epithelial defects; corneal transplantation; limbal stem cell deficiency; laser eye surgery (especially laser assisted vision correction procedures such as photorefractive keratectomy (PRK), laser-assisted sub-epithelial keratectomy (LASEK) and laser-assisted in situ keratomileusis (LASIK)); Stevens-Johnson-Syndrome; recurrent corneal erosions; superficial punctate keratitis (SPK); glaucoma; and surgical lesions.

13. Ophthalmic solution for use according to any of the preceding claims, wherein said pharmaceutically acceptable salt is selected from the group consisting of salts of organic acids such as acetic, citric, formic and tartaric acid, and salts of mineral acids such as HCl and H₂SO₄.

14. Ophthalmic solution for use according to any of the preceding claims, wherein the N-(N-acetylcysteinyl-)chitosan has a content of free thiol groups in an amount of from 105 µmol/g polymer to 250 µmol/g polymer, preferably of from 110 µmol/g polymer to 250 µmol/g polymer, most preferably of from preferably 140 to 250 µmol/g polymer.

15. Ophthalmic solution for use according to any of the preceding claims, wherein the amount of crosslinked thiol groups in the N-(N-acetylcysteinyl-)chitosan is 30% or less of the total thiol groups therein, preferably 25% or less, most preferably 15% or less.
16. A method of treatment and prevention of a non-infectious corneal disorder, wherein a sterile aqueous ophthalmic solution comprising N-(N-acetylcysteinyl-)chitosan as defined in any one of the preceding claims is applied as defined in any of the preceding claims.
## INTERNATIONAL SEARCH REPORT

### 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

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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, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
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Cortes Suarez, Jose
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