

**COMPOSITION AND USE OF AN OPHTHALMIC SOLUTION BASED ON
HYALURONIC ACID AND ARABINOGALACTAN**

DESCRIPTION

Field of the invention

The present invention relates to the medical-pharmaceutical field, and more precisely to preparations for topical ophthalmic use (eye drops), in particular an ophthalmic composition comprising a hyaluronic acid and arabinogalactan association. The invention also relates to an ophthalmic composition in combination with panthenol, vitamin E-D- α -polyethylene-glycol (TGPS) and trehalose. Both compositions can be applied to the ocular surface in order to ensure a significant and lasting reduction of dry-eye syndrome, and of the general inflammatory ocular state, with good local tolerability.

Background of the invention

Dry-eye syndrome, or kerato conjunctivitis sicca, is a common eye disease which affects millions of people, caused by chronic dehydration of the conjunctiva and cornea, which causes irritation. It is mainly due to a quantitative reduction or qualitative alteration of the tear film which covers the eye and normally lubricates and protects it. Poor production or excessive evaporation of tears may be a complication of blepharitis, conjunctivitis (including allergic forms) and other inflammatory eye diseases. Dry-eye syndrome can also be the result of systemic diseases such as Sjögren's syndrome, systemic lupus erythematosus and

rheumatoid arthritis. Furthermore, the disorder is typical in advanced age (due to tear gland atrophy), in women experiencing menopause (due to new hormonal balances) and in those with prolonged use of contact
5 lenses, eye drops or certain systemic drugs (antihypertensives, anxiolytics, sleeping pills, antihistamines and many others).

Without going into the details of the etiology thereof, it has been shown that dry-eye syndrome and
10 anomalies in the corneal tear film, including subsequent inflammatory changes in the entire ocular surface, are able to affect the whole eye including ocular adnexa, conjunctiva and cornea.

Although often regarded as a secondary problem,
15 kerato conjutivitis sicca, commonly referred to as dry-eye syndrome, is becoming a growing health problem, affecting 17% of women and 11% of men in the United States alone (Burgalassi et al., 2011. Curr Eye Res. 36(1):21-8). These data are underestimated when
20 considering patients who do not undergo treatment and those who self-treat and/or have intermittent symptoms and mild symptoms.

Recently, the International Dry Eye Workshop (DEWS) defined dry-eye syndrome as "a multifactorial
25 tear and ocular surface disease which results in symptoms of discomfort, visual disturbances, and tear instability with potential damage to the ocular surface which is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".

30 The role of an inflammatory component in dry-eye

syndrome is known (Baudoin et al., 2018. Acta Ophthalmol 96(2): 111-119; Vazirani, 2018. Indian J Ophthalmol 66(1): 44; Yagci and Gurdal, 2014. Int Ophthalmol. 34(6):1291-1301). In fact, several
5 biochemical factors are known, specifically some enzymes which are behind this phenomenon, such as the enzymatic cascade of cyclooxygenases (COX), to which the prostaglandin family belongs, and other enzymes such as the enzymatic complex of xanthine
10 oxidoreductase and xanthine oxidase, present in the human cornea (Cejkova et al., 2007. Histol Histopathol 22(9):997-1003;).

In particular, xanthine dehydrogenase + xanthine oxidase is an enzymatic system which catalyzes the
15 oxidation of hypoxanthine to xanthine, consequently producing uric acid. The enzymatic complex exists in two separate but interconvertible forms, xanthine dehydrogenase and xanthine oxidase, which generates/generate reactive oxygen species (ROS),
20 aggravating factors of tissue damage, such as occurs in myocardial tissue following the ischemic or reperfusion phenomenon. However, this pathological situation is not limited to myocardial tissue but is present in other tissues and/or organs such as, for example, the ocular
25 tissues and in particular the cornea (Cejkova et al., 2007. Histol Histopathol 22(9):997-1003; Kuppusamy and Zweier, 1989 The Journal of biological chemistry 264:9880-9884; Sery and Petrillo, 1984. Journal of current eye research 1:243-252; Pustivrh et al., 2000.
30 Reproduction, fertility and development 12(6):269-275).

In particular, it has been shown that xanthine oxidase plays a key role in inflammatory processes and cytotoxicity triggered by the production of superoxide anion and also for the conversion thereof into oxygen
5 peroxide. In fact, it has been shown that XO is an enzyme involved in dry-eye syndrome, in particular in oxidative reactions on the ocular surface of patients affected by Sjögren's syndrome with dry-eye syndrome.

Background art

10 With the recognition of the role of inflammation in dry-eye syndrome, several new treatments have been studied with the aim of inhibiting the various inflammation pathways. The current medications used, which have shown an effective role in managing the
15 syndrome, include cyclosporine A, corticosteroids, *tracolumus*, derivatives of tetracyclines and autologous serum.

However, it should once again be emphasized that dry-eye syndrome is a multifactorial disease, on the
20 one hand linked to the instability of the tear film and hyperosmolarity, which can be considered physical-chemical parameters, and on the other to more biological parameters such as inflammation.

Patent document WO 2009/018060 describes an
25 ophthalmic composition comprising one or more terpene compounds, and one or more natural polymers selected from the group comprising hyaluronic acid, chondroitin sulfate, alginate, guar gum, fructan, arabinogalactan or any of the corresponding salts or derivatives
30 thereof. In particular, the document does not take into

account the simultaneous use of hyaluronic acid and arabinogalactan, and the field of application thereof remains limited to the use of the ophthalmic composition as a liquid for the care and disinfection
5 of contact lenses or for eye drops for irritated eyes. There is no reference to either use in the treatment of dry-eye syndrome or the combined use of hyaluronic acid and arabinogalactan.

European patent EP 1912707 relates to an
10 ophthalmic composition containing a mucus adhesive polysaccharide capable of promoting the re-epithelialization of the cornea. More specifically, an ophthalmic solution containing arabinogalactan, to be used as artificial tears to stimulate the recovery of
15 corneal lesions, especially for people who use contact lenses.

Also in this case the field of application does not take into consideration dry-eye syndrome, neither from the point of view of the chemical-physical
20 parameters, such as the instability of the tear film and hyperosmolarity, nor of the biological parameters, such as inflammation. Furthermore, the composition does not include the presence of hyaluronic acid as an active ingredient.

25 Although the multifactoriality of dry-eye syndrome is known and the studies on the delicate regulatory balance of corneal tear film stability have clarified the etiology and role of the inflammatory component in the course of the disease, the need remains to date for
30 an ophthalmic formulation for use in the treatment of

dry-eye syndrome which considers both tear film instability and the role of inflammation.

Furthermore, in the literature it is known that some plants commonly used by Native Americans have healing effects: in particular, it has been shown that extracts of some plants such as *Larix laricina* affect xanthine oxidase activity (Owen and Johns, 1999. J Ethnopharmacol. 64(2):149-160). However, it should be emphasized that the use of *Larix laricina* extracts has been proposed to a limited extent for the treatment of gout, with an exclusively oral formulation and administration, and without any indication of the anti-inflammatory effect in the broad sense.

The present invention proposes for the first time the use of hyaluronic acid in combination with arabinogalactan in an ophthalmic composition for the treatment of dry-eye syndrome, accompanied by inflammatory phenomena, linked at least in part to the action of the enzyme system xanthine dehydrogenase/xanthine oxidase, the activity of which is unexpectedly reduced thanks to the combined action of the two active ingredients: hyaluronic acid and arabinogalactan. From the same combined action of these two active ingredients comes the fact that the factors underlying the inflammatory phenomena are also reduced, at least in part.

Summary of the invention

A first object of the present invention is the formulation of an ophthalmic composition comprising hyaluronic acid and arabinogalactan, for use in the

treatment of dry-eye syndrome.

Another object of the invention is the use of the combination of hyaluronic acid and arabinogalactan with the addition of panthenol, vitamin E-D- α -polyethylene glycol (TGPS) and trehalose, for ophthalmic
5 compositions in the form of a hypotonic aqueous solution, with neutral pH and without preservatives, for use in the treatment of dry-eye syndrome.

It is another object of the present invention to
10 provide an ophthalmic composition based on hyaluronic acid and arabinogalactan, with the addition of panthenol, vitamin E-TGPS and trehalose for the treatment of dry-eye syndrome even if accompanied by inflammatory phenomena which are often connected
15 thereto.

It is another object of the present invention to provide an ophthalmic composition based on hyaluronic acid and arabinogalactan, with the addition of panthenol, vitamin E-TGPS and trehalose, which for the
20 addition of a gelling agent, such as Poloxamer 407, is in the form of a gel, for the treatment of dry-eye syndrome even if accompanied by inflammatory phenomena which are often connected thereto.

It is another object of the invention to provide a
25 method for the treatment of an inflammatory process dependent, at least in part, on the activity of the enzyme system xanthine dehydrogenase-xanthine oxidase by means of the topical application of the ophthalmic composition described herein comprising hyaluronic acid
30 and arabinogalactan, and possibly also panthenol,

vitamin E-TGPS and trehalose.

Detailed description of the invention

The present invention relates to an ophthalmic composition based on hyaluronic acid and arabinogalactan for use in the protection, hydration, and lubrication of the eyes. Furthermore, the object of the present invention is an ophthalmic composition based on hyaluronic acid and arabinogalactan for the treatment of dry-eye syndrome, and the inflammatory state often associated therewith. According to a preferred embodiment, the composition of the present invention is a hypotonic aqueous ophthalmic solution with neutral pH and free of preservatives. In addition to hyaluronic acid and arabinogalactan, it further comprises panthenol, trehalose and Vitamin E-TGPS.

In literature there are several ophthalmic compositions for the treatment of dry-eye syndrome, but none of them includes a composition based on hyaluronic acid and arabinogalactan, comprising panthenol, vitamin E-TGPS and trehalose. Furthermore, ophthalmic compositions are not currently disclosed which provide an ophthalmic formulation for use in the treatment of dry-eye syndrome which considers both the chemical-physical parameters of the syndrome, such as tear film instability and hyperosmolarity, as well as biological ones such as the role of inflammation, and in particular the activity of the xanthine oxidase system.

Patent documents WO 2009/018060 and EP 1912707 describe, respectively, an ophthalmic composition comprising one or more terpene compounds, and one or

more natural polymers (selected from the group comprising hyaluronic acid, chondroitin sulfate, alginate, guar gum, fructan, arabinogalactan or any of the corresponding salts or derivatives thereof) and an
5 ophthalmic composition capable of promoting the re-epithelialization of the cornea containing arabinogalactan.

However, dry-eye syndrome is not included in the field of application thereof, neither from the point of
10 view of chemical-physical parameters such as tear film instability and hyperosmolarity, and of more biological parameters such as inflammation.

As reported above, the use of extracts of *Larix laricina* for the treatment of gout is known in the
15 literature (Owen and Johns, 1999. J Ethnopharmacol. 64(2):149-160). This indication proposed only and exclusively for the treatment of gout does not take into consideration the ophthalmic district, nor does it consider anti-inflammatory effects.

20 On the other hand, the authors of the present invention have evaluated, for the first time, on the basis of the experimental tests reported below, the potential capacity of arabinogalactan and hyaluronic acid, first individually and then in association with
25 each other with a synergistic effect, to interfere with the activity of xanthine oxidase, for the purpose of a curative/soothing ophthalmic use in syndromes with an inflammatory component which depends at least in part on the presence of xanthine oxidase.

30 In detail, a first object of the present invention

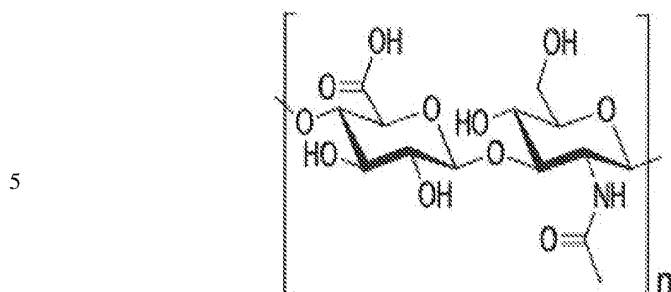
is an ophthalmic solution based on hyaluronic acid and arabinogalactan and the synergistic effect thereof in the inhibition of xanthine oxidase.

Another object of the invention is an ophthalmic
5 composition in which the association of hyaluronic acid and arabinogalactan is accompanied by panthenol, trehalose and Vitamin E-TGPS.

A first of the fundamental and characterizing components of the ophthalmic solution according to the
10 present invention is hyaluronic acid, in the form of sodium hyaluronate, an anionic glucosaminoglycan widely distributed in connective, epithelial and neuronal tissues. It can be a very large molecule with a variable size depending on the tissue and body area.
15 For example, the hyaluronic acid present in the human synovium is on average 7 million Dalton (Da) per molecule, or about 20,000 disaccharide monomers, while in other areas the size thereof is less than about 3-4 million Da. Hyaluronic acid is essentially a long chain
20 of carbohydrates capable of recruiting and binding water molecules in a ratio equal to 1000 times the weight thereof.

Given that ocular tissues require optimal fluid levels for the proper physiology and functioning
25 thereof, it is not surprising that hyaluronic acid forms 95% of the fluids within the eye, supporting the health of the ocular structures such as the cornea and retina. As hyaluronic acid is a polysaccharide with properties to preserve and retain water, it offers high
30 hydration and lubrication of the corneal surface.

The chemical structure thereof is as follows:



Hyaluronic (HA) disaccharide (composed of
d-glucuronic acid and N-acetyl-d-glucosamine)

10 The concentration of hyaluronic acid in the solutions according to the present invention ranges from 0.1% w/w to 0.5% w/w, and more preferably from 0.15% w/w to 0.3% w/w.

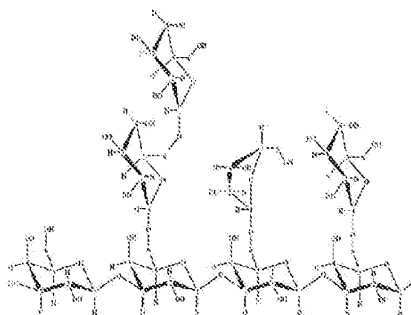
A second fundamental and characterizing component
15 of the solutions of the present invention is arabinogalactan, a natural mucopolysaccharide extracted from the bark of the Canadian Larch, even if in nature a second class of arabinogalactan derived from microbial populations can be found. It is a biopolymer
20 consisting of the monosaccharides arabinose and galactose. Arabinogalactan exhibits non-viscous Newtonian behavior, as shown by the fact that a concentration as high as 10% w/w has a viscosity of 1.6 mPa.s, and has excellent mucus adhesive properties,
25 useful for permanence on the ocular surface.

It is known in the literature that arabinogalactan with a concentration of at least 5% w/w exerts a good protective effect against the appearance of dry corneal areas. Furthermore, it significantly reduces the

healing time of an experimental corneal lesion as early as 27 hours after the first treatment. It can therefore be considered a therapeutic product for the protection of dry-eye syndrome and for the treatment of corneal wounds (1,2,3).

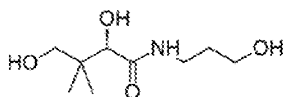
However, the concentration of arabinogalactan in the solutions according to the present invention ranges from 0.30% w/w to 1.00% w/w, and more preferably from 0.4% w/w to 0.8% p/p. The chemical structure thereof is as follows:

15 **Arabinogalacta**



Furthermore, the ophthalmic composition of the present invention includes D-panthenol as a component. The latter is an alcohol analogue of pantothenic acid (Vitamin B5), and therefore can be considered as pro-vitamin B5. It is rapidly oxidized to pantothenic acid in organisms. D-panthenol at room temperature is a clear viscous liquid and is used in cosmetic and drug products as a moisturizer and to improve wound healing. Sometimes conditions such as dry-eye syndrome can cause abrasions; in particular, those associated with the cornea induce particularly annoying symptoms such as tearing, redness, pain, stiffness, and blurred vision.

The study conducted by Islam Mahmoud Hamdi (Effect of D-Panthenol on corneal epithelial healing after surface laser ablation. 2018. Journal of Ophthalmology) demonstrated a positive effect of panthenol on the healing of the corneal epithelium after laser ablation. The chemical structure thereof is as follows:



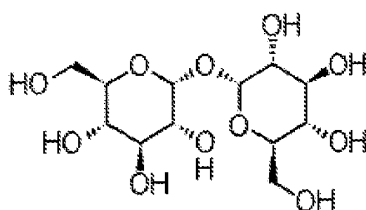
Panthenol

Panthenol rapidly penetrates into the skin and mucous membranes (including the intestinal membrane), where it is rapidly oxidized to pantothenic acid. This acid is particularly hygroscopic, in fact it binds water very effectively. It is also used in the biosynthesis of coenzyme A, which plays a fundamental role in a wide range of enzymatic reactions and in cell growth. Panthenol is present in the two D-/L-enantiomers thereof, but only D-panthenol (dexpanthenol) is biologically active. However, both forms have moisturizing properties. For cosmetic use, panthenol can be either in the D- form thereof, or as a racemic mixture D-/L- (DL-panthenol).

The concentration of panthenol in the solutions according to the present invention ranges from 0.150% w/w to 0.80% w/w, and more preferably from 0.30% w/w to 0.5% w/w.

Another ingredient characterizing the ophthalmic composition of the present invention is trehalose, a disaccharide with protective and stabilizing properties of cell membranes, as well as antioxidant. Trehalose is
5 formed from two monomers of α -glucose by means of a 1,1-glycosidic bond, giving it the name α -D-glucopyranosyl-(1 $\rightarrow$ 1)- α -D-glucopyranoside. This bond makes trehalose very resistant to acid hydrolysis, and therefore it is stable in solution at high
10 temperatures, even in strongly acidic conditions.

The chemical structure thereof is as follows:



15

Trehalose

Furthermore, trehalose has remarkable water retention abilities, it safeguards the lipid bilayer during dehydration and rehydration by replacing water,
20 forming hydrogen bonds between the -OH groups thereof and the groups of the lipid heads. Several studies (Tange et al. 2007. J Magn Reson 2007 184(2):222-227; Li et al. 2012. Molecular Vision 16:317-329) have demonstrated the efficacy and safety of trehalose as
25 ophthalmic drops for the treatment of moderate to severe dry-eye syndrome.

The concentration of trehalose in the solutions according to the present invention ranges from 2.00% w/w to 5% w/w, and more preferably from 3% w/w to 4%

syndrome condition which comprises the administration of an effective therapeutic amount of a composition comprising hyaluronic acid and arabinogalactan comprising panthenol, trehalose and vitamin E-TGPS in
5 such amounts and for a time such as to induce the desired effect.

The compositions are administered in any amount and by any route of administration suitable for ocular treatment. The exact dosage will be chosen by the
10 physician according to the state of the patient to be treated. Dosage and administration will be tailored to provide sufficient active ingredient levels or to maintain the desired effect. Additional factors which may be considered comprise the severity of the
15 condition, course of the disease, age, weight and gender of the patient, administration timing and frequency, diet, combination with other drugs, sensitivity reactions, tolerance and response to therapy.

20 The active ingredients and components of the invention are formulated in a form suitable for topical application in the eye, preferably in the form of eye drops, instillable in drops, each drop consisting of a form of dosage unit so as to allow easy administration
25 and dosage uniformity.

It is understood how the dry-eye syndrome treatment method according to the present invention is not limited in the use thereof in humans, but the use thereof can also be extended to all mammals.

30 **Pharmaceutical forms and dosages of the composition in**

object**Pharmaceutical compositions**

Pharmaceutical compositions comprising hyaluronic acid and arabinogalactan are provided in one aspect of the present invention. Compositions further comprising panthenol, vitamin E-TGPS and trehalose are also provided. In some embodiments such compositions may comprise one or more additional therapeutic agents, selected from the group comprising growth factors, anti-inflammatory agents, vitamins, fibronectin and collagen, amino acids, polysaccharides and various buffer systems such as phosphate, citrate and tris.

The ophthalmic composition according to the present invention can be prepared in any pharmaceutical form which allows the corneal application thereof, such as eye drops, gels, ointments, but preferably it is prepared in the form of eye drops sterile by filtration at 0.2 microns. This is because the sterilization with flowing steam at 121°C for at least 15 minutes, as prescribed by the pharmacopoeia, is deleterious for the stability of the eye drops, especially with regard to some components such as vitamins and hyaluronic acid.

The ophthalmic composition may comprise one or more additional therapeutic agents, selected from the group comprising growth factors, anti-inflammatory agents, vitamins, fibronectin and collagen, amino acids, polysaccharides, and various buffer systems such as phosphate, citrate, and tris.

EXAMPLES

Basic formulations are now reported for

illustrative purposes, without however being a limitation to the invention. Other aspects, advantages, or modifications within the scope of the invention will become apparent to those skilled in the art pertaining
5 to the invention.

BASIC formula according to the invention:
hyaluronic acid and arabinogalactan association
and borate buffer.

10 The basic formula of the eye drops according to the present invention is reported in the following Table 1:

Table 1. Basic eye drops formula

BASIC formulation	% w/w
Hyaluronic acid sodium salt	0.15
Arabinogalactan	0.40
Boric Acid	0.852
Sodium tetraborate decahydrate	0.137

15

According to an aspect of the invention, the BASIC formula of Table 1 has been suitably implemented with some specific ingredients to obtain a formulation in the form of eye drops as reported in Table 2, which
20 forms a preferred embodiment of the invention.

Table 2. Preferred formula of the five-component eye drops (hyaluronic acid and arabinogalactan association + panthenol, trehalose, and Vitamin E-TGPS)
25

Basic formulation Eye drops	% w/w	Action	# CAS
Hyaluronic acid sodium salt	0.15 - 0.4	Viscous moisturizing agent	
Arabinogalactan	0.40 - 1.00	Immunostimulating re- epithelialization agent	
Panthenol	0.30 - 0.60	Anti-inflammatory emollient	
Trehalose	3.00 - 4.00	Membrane stabilizing agent and osmolality	
Vitamin E-TGPS	0.030	Antioxidant stabilizing the tear film	
Boric Acid	0.852	Buffer	
Sodium tetraborate decahydrate	0.137	Buffer	
Distilled water	Up to 100		
Sterile by filtration 0.2μ	Yes		

Following the experimentation carried out, the formulation of particularly preferred eye drops according to the invention was defined, as reported in 5 the following Table 3. These eye drops are identified below by the letter **A**.

Table 3.
Effective formulation of the eye drops **A**

Formulation A	% w/w
Hyaluronic acid sodium salt	0.15
Arabinogalactan	0.40
Panthenol	0.30
Vitamin E-TGPS	0.030
Trehalose	3.0
Boric Acid	0.852
Sodium tetraborate decahydrate	0.137
Osmolality mOsm/kg	240–270 hypotonic

Sterile by filtration at 0.2 μ	Yes
------------------------------------	-----

The solution thus obtained is clear in appearance, has a neutral pH ranging from 6.8 to 7.6, and an osmolality in the range of 240–270 mOsm/kg, thus resulting slightly hypotonic.

5 Said solution is then easily sterilized by filtration (0.2 microns), also in consideration of the action of the arabinogalactan which seems to dilute the hyaluronic acid, making the eye drops less viscous, albeit in a limited way.

10 **Preparation method**

The preparation method is not particular in itself, and involves steps known to those skilled in the art. However, as is known to those skilled in the art, normally when polysaccharide structures are mixed
15 with hyaluronic acid, a common increase in viscosity is found.

Surprisingly, the solubilization of the various components of the eye drops of the invention is not difficult. The presence of arabinogalactan makes the
20 solution particularly easy to filter at 0.2 μ m, as the latter has the ability to decrease the viscosity of the hyaluronic acid and therefore also of the final eye drops, avoiding possible expected increases of the viscosity.

25 Finally, according to another aspect of the invention, with the addition of a gelling agent such as Poloxamer 407 for a concentration range between 1% and 9% by weight, to the solution having the composition of Table 3, a gel was obtained before sterilization by

filtration, which was much more viscous than the eye drops, still for ophthalmic use, while maintaining the synergistic effects of the AG + HA association, on the xanthine oxidase activity.

5 **EXPERIMENTAL PART**

As noted above, dry-eye syndrome is a multifactorial syndrome with a marked inflammatory component. Some enzymes, such as COX and XO, which reside upstream of the inflammatory cascade are
10 strongly involved in the course of the syndrome; in particular, XO is an enzyme involved in dry-eye syndrome in patients with Sjorgen's syndrome.

Starting from the above considerations, the experimental activity first involved the evaluation of
15 the potential capacity to interfere with the xanthine oxidase activity of the BASIC formulation containing hyaluronic acid and arabinogalactan in borate buffer.

In particular, arabinogalactan, probable constituent of larch extracts, proposed as anti-gout
20 agents, and therefore possible XOD activity inhibitors, was evaluated. In fact, this evaluation was carried out for arabinogalactan, for hyaluronic acid and for the association thereof.

The enzymatic reaction, which is reported for
25 clarity, consists of:

Xanthine oxidase + Xanthine → Uric acid

Arabinogalactan or hyaluronic acid or
arabinogalactan with hyaluronic acid were added to this
reaction. Given the positive results, this evaluation
30 was extended to the eye drops formulation in the

entirety thereof comprising panthenol, vitamin E-TGPS and trehalose. Also in this case the same xanthine oxidase activity inhibition was obtained, confirming the anti-inflammatory potential of the eye drops of the
5 present invention.

Furthermore, since the product of xanthine oxidase is both uric acid and superoxide anion $O_2^{\cdot-}$, the ability to inhibit the formation of the latter was evaluated for arabinogalactan, for hyaluronic acid and for the
10 association thereof.

Any inhibition is particularly important because the superoxide anion production is at the origin, at least in part, of the inflammatory phenomena of the ocular surface. The superoxide anion produced by
15 xanthine oxidase in the oxidation reaction of xanthine was detected by the reduction of **ferrocytochrome c** to **ferrocytochrome c** by the same superoxide anion ($O_2^{\cdot-}$) (Fridovich). The reaction is reported here for clarity:



Arabinogalactan or hyaluronic acid or arabinogalactan with hyaluronic acid were added to this reaction. Furthermore, given the positive results, this evaluation was extended to the eye drops formulation in
25 the entirety thereof comprising panthenol, vitamin E-TGPS, trehalose. Also in this case the same xanthine oxidase activity inhibition was obtained, confirming the anti-inflammatory potential of the eye drops of the present invention.

30 Finally, chemical-physical parameters

characterizing the formulation of the ophthalmic composition of the present invention were evaluated, by carrying out rheology measurements. This was done to explain and confirm the interaction between
5 arabinogalactan and hyaluronic acid as much as possible. Specifically, the chemical-physical rheological parameters analyzed were the storage modulus g' (elastic modulus) with the loss modulus g'' (viscous modulus) and viscosity (pa.s) as such.

10 All with the aim of characterizing the arabinogalactan + hyaluronic acid association and the eye drops derived therefrom and of the present invention, containing, in addition to arabinogalactan and hyaluronic acid, panthenol, vitamin E-TGPS, and
15 trehalose.

Verification of the xanthine oxidase (XOD) reaction inhibition and formation of uric acid

Materials and Methods

The effect of arabinogalactan, hyaluronic acid and
20 the association thereof was investigated by monitoring the formation of uric acid over time (0, 1, 5, 10, 15, 30 min). Uric acid concentration was determined at 291 nm using a DR6000 UV spectrophotometer (Hach, Lange). The absorbance value is related to the concentration by
25 means of the Lambert-Beer law:

$$A = \varepsilon bC$$

where A is the absorbance of uric acid at 291 nm, ε is
30 the molar absorption coefficient, b is the optical path

(thickness of the cuvette in which the solution is contained) and C is the uric acid concentration.

The blank/control consists of: 50 μM xanthine, 10 mg L^{-1} of xanthine oxidase (XO) (0.00016 μUI of enzyme) in borate buffer solution (see table 3) $7.2 \leq \text{pH} \leq 7.8$). The effect of the components of the eye drops was investigated by adding the individual components to the blank solution: respectively

- (i) 0.4% (w/w) of arabinogalactan (AG)
- (ii) 0.15% (w/w) of hyaluronic acid (HA)
- (iii) association of 0.4% (w/w) of AG + 0.15% (w/w) of HA (mix AG + HA).
- (iiii) Eye drops corresponding to the formulation of Tab.3.

All the tests were conducted at least in triplicate.

The uric acid formation reductions were calculated as:

$$\text{Reduction \%} = 100 - \left(\frac{C_{30-i}}{C_{30-\text{control}}} * 100 \right)$$

where C_{30-i} is the final concentration (30 min) of uric acid in the i-th test and $C_{30-\text{control}}$ is the uric acid concentration at 30 min in the blank (control).

Furthermore, the inhibition evaluation reported above was also carried out in borate buffer for arabinogalactan, for hyaluronic acid and for the association thereof, and finally for the eye drops formulation of the present invention, also comprising panthenol, vitamin E- TGPS and trehalose.

Results and Discussion

The results are summarized in Table 4 and in the graphs below.

TABLE 4

Inhibition of xanthine oxidase activity: Inhibition of uric acid production

	Blank	i	ii	iii
	XOD reaction Uric acid μ M	XOD + Arabinogalactan reaction Uric acid μ M	XOD + Hyaluronic Acid reaction Uric acid (μ M)	XOD + Arabinogalactan reaction + Hyaluronic acid Uric acid
R2*	0.93	0.99	0.99	0.91
Inhibition %	-	27	0	39
μ M produced in 30 minutes	15.3	11.4	15.3	10
μ M produced per minute	0.51	0.38	0.51	0.35

- R2 was calculated assuming/approximating a linear oxidation kinetics of xanthine to uric acid.

T minutes

10 Average of three determinations

The AG and AG/HA association cause a statistically significant decrease in uric acid compared to the blank, respectively 26%, 39%. In particular, as can be seen in Fig. 1b, the presence of hyaluronic acid has no effect on the formation of uric acid (0% inhibition). On the other hand, the fact that the percentage of uric acid is reduced by the AG+HA association to a greater extent than the solution containing the AG alone suggests a possible synergistic effect on the inhibition by AG and HA against the enzyme xanthine oxidase or a possible interaction block between the enzyme xanthine oxidase and the substrate thereof, xanthine.

Due to the shape thereof, arabinogalactan could have a sequestering capacity for the enzyme xanthine oxidase and/or could mask the substrate (xanthine) to the enzyme. It has been observed that the combination
 5 of arabinogalactan and hyaluronic acid exerts and enhances the same effect regardless of the inhibition mechanism. This has its own experimental validity and an unexpected and innovative statistical significance.

Moreover, the same results were also obtained when
 10 the eye drops formulation of the present invention was evaluated, comprising, in addition to arabinogalactan and hyaluronic acid, also panthenol, vitamin E-TGPS and trehalose. The results confirmed the same inhibitory capacity: in fact, it goes from an inhibition of 38% in
 15 the case of the hyaluronic acid + arabinogalactan association to a slightly higher value, specifically 45%.

Table 5 follows.

20

Table 5

Inhibition of xanthine oxidase activity: inhibition of uric acid production due to the effect of the eye drops. (iii)

	XOD reaction Uric acid μM	XOD reaction + Eye drops Uric acid μM
R2*	0.93	0.99
Inhibition %	-	45
μM produced in 30 minutes	15.3	8.4
μM produced per minute	0.51	0.28

Verification of superoxide anion production inhibition
due to the effect of xanthine oxidase

Materials and Methods

The effect of arabinogalactan, hyaluronic acid,
5 and the association thereof on superoxide anion
production over time (0, 1, 5, 10, 15, 30 min) was
investigated. The production of superoxide anion was
determined by the reduction of **ferrocytochrome C (3+)**
to **ferrocytochrome C (2+)**, monitoring absorption at 551
10 nm using a DR6000 UV spectrophotometer (Hach, Lange).
The tests for the determination of superoxide anion
production were carried out still using the xanthine
oxidase reaction used previously.

Produced by the superoxide anion, the
15 ferrocytochrome C was calculated considering a molar
absorption equal to $2.1 \times 10^4 \text{ M}^{-1} \cdot \text{cm}^{-1}$ (Ref.16-17). The
superoxide inhibition evaluation reported above was
performed for arabinogalactan, hyaluronic acid, and the
association thereof. Furthermore, the eye drops
20 formulation of the present invention was also
evaluated, also comprising panthenol, vitamin E-TGPS
and trehalose.

Results and Discussion

The data on the inhibition capacity of superoxide
25 anion production are summarized in Table 6 and in the
graphs relating to the inhibition kinetics, shown in
the accompanying figures in which:

figures 1a-c relate to the kinetics of uric acid
formation, with the uric acid concentration [μM] vs
30 time [min] in the absence of components (control/blank)

and in the presence of (a) arabinogalactan (AG), (b) hyaluronic acid (HA) and (c) arabinogalactan and hyaluronic acid (AG + HA);

Figures 2a-c relate to the kinetics of ferrocytochrome C formation, with the absorption of the ferrocytochrome [abs] vs time [min] in the absence of components (control/blank) and in the presence of: (a) arabinogalactan (AG), (b) hyaluronic acid (HA) and (c) arabinogalactan and hyaluronic acid (AG + HA);

fig. 3 is a graph of the trend of G'' (**Loss Modulus Viscosity**) of hyaluronic acid 0.15%, hyaluronic acid 0.15% + arabinogalactan 0.4% and arabinogalactan at 0.4%.

TABLE 6

	Blank	i	ii	iii
	Control Production Fe^{+2} Cit.C	Reaction with Arabinogalactan Production Fe^{+2} Cit.C	Reaction with Hyaluronic acid Production Fe^{+2} Cit.C	Reaction with Arabinogalactan + Hyaluronic Acid Production Fe^{+2} Cit.C
R^{2*}	0.99	0.99	0.74	0.98
Inhibition %	0	38.1	17.2	61.8
μM produced in 30 minutes	15.3	9.3	12.6	5.91
μM produced per minute	0.51	0.31	0.42	0.197

From the data obtained it is clear that the inhibition of xanthine oxidase activity, by arabinogalactan, hyaluronic acid and even more by the association thereof, has a first confirmation in the inhibition of uric acid, but also has a second, even more significant and important finding in the

inhibition of superoxide anion production. Furthermore, referring to the inhibition of superoxide anion production, it is noted how the addition of hyaluronic acid to arabinogalactan, which is undoubtedly the major architect of the inhibitory effect, increases this inhibitory effect. What is reported, however it can be explained, whatever the underlying mechanism is, is new and useful from the pharmacological point of view, with reference to inflammatory phenomena in which there is even partial participation of xanthine oxidase.

Furthermore, the same results were also obtained when the eye drops formulation of the present invention was evaluated, comprising, in addition to arabinogalactan and hyaluronic acid, also panthenol, vitamin E-TGPS and trehalose. The results reported in Table 7 confirmed the same inhibitory capacity.

TABLE 7

	Control Fe ⁺² Cit.C production	Reaction with Eye drops Fe ⁺² Cit.C production
R ² *	0.99	0.98
Inhibition %	0	65.0
μM produced in 30 minutes	2.25	1.02
\	0.098	0.034

20 **Rheological characterization of the formulation of the present invention.**

In addition to the evaluation of the effect of arabinogalactan, hyaluronic acid and the association thereof on xanthine oxidase activity and in order to

characterize the possible interaction thereof, to justify the inhibitory effect thereof, rheology measurements were carried out with the hypothesis that the two macrostructures, arabinogalactan on the one
5 hand and hyaluronic acid on the other, could modify the rheological trend of the formulation of the present invention.

MATERIALS AND METHODS

With reference to fig. 3, the characterization of
10 the following solutions was carried out using an AM Instruments Plate Viscometer, in Oscillation Mode. The following solutions were measured:

Sample 1: Hyaluronic acid solution at
0,15% w/w

15 **Sample 2:** Arabinogalactan solution 0.4% +
Hyaluronic acid 0.15% w/v

Sample 3: Arabinogalactan solution 0.4% w/w.

First Point

The graph shown in figure 3 shows the trend
20 of G'' (Loss Modulus viscosity) of the three solutions:

Solution no. 1: Hyaluronic acid 0.15% w/w

Solution no. 2: Arabinogalactan 0.4% +
hyaluronic acid 0.15% w/w

25 Solution no. 3: Arabinogalactan 0.4% w/w

Interpretation of the Results:

The measurements in oscillation mode related to G'' indicated that:

Solution no. 1: Hyaluronic acid 0.15% w/w has a
30 linear modulus G'' (Loss Modulus Viscosity), typical of

a Newtonian product, always with a value higher than the other measured solutions;

Solution no. 2: Arabinogalactan 0.4% + Hyaluronic acid 0.15% w/w has a modulus G'' (Loss Modulus Viscosity) with a linear trend, typical of a Newtonian product, parallel to but slightly lower than Solution no. 1

Solution no. 3: Arabinogalactan 0.4% has a non-linear modulus G'' (Loss Modulus Viscosity), always much lower than the other Solutions 1 and 2.

From what has been said, it is clear how unexpectedly the presence of arabinogalactan causes the modulus G'' (viscosity) of hyaluronic acid to decrease.

The measured value can be expressed as follows:

Hyaluronic Acid G'' > Arabinogalactan + Hyaluronic Acid G'' > Arabinogalactan

Secondo Point

The graph in fig. 3 shows the trend of G' (Storage Modulus elasticity) of the three solutions:

Solution no. 1: Hyaluronic acid 0.15% w/w

Solution no. 2: Arabinogalactan 0.4% + Hyaluronic acid 0.15% w/w;

Solution no. 3: Arabinogalactan 0.4% w/w.

Interpretation of the Results:

The measurements in oscillation mode related to G' indicate that the three solutions have a low G' value and therefore low elasticity value.

From the data obtained, it can be noted that the viscosity of arabinogalactan is particularly low; the molecule does not have any rheological properties such

as viscosity and elasticity. Hyaluronic acid has good viscosity even if not at high concentrations and behaves like a Newtonian fluid.

The association of arabinogalactan + hyaluronic acid does not lead, as one might expect, to an increase in the viscosity of the AG + HA mixture compared to hyaluronic acid alone, but on the contrary, a slight decrease in viscosity is observed, which is surprising, since usually the addition of polysaccharides to a hyaluronic acid solution does not decrease the viscosity of the polymer but increases it or, at least, keeps it unchanged.

On the other hand, it seems that the addition of arabinogalactan has a slight diluting capacity on the hyaluronic acid concentration. This result, frankly unexpected, even if numerically not very relevant, can further support the hypothesis of a particular interaction between arabinogalactan and hyaluronic acid, confirming, albeit indirectly, the synergy between the two active ingredients already observed at the enzymatic reaction level, in particular with inhibitory capacity on the xanthine oxidase reaction.

Given the results obtained, the characterization was further extended to determine the viscosity as a function of the shear rate, always using a Plate Viscometer, in particular the following solutions were measured.

Sample 1: Hyaluronic acid

Sample 2: Hyaluronic acid + Arabinogalactan

Sample 3: Eye drops A

Sample 4: Arabinogalactan

Interpretation of the Graph (Fig. 4)

- 1: Hyaluronic acid: linear trend (Newtonian)
higher viscosity; linear trend (Newtonian)
5 viscosity;
2: Hyaluronic Acid + Arabinogalactan: lower than
the previous one;
3: Complete eye drops: linear trend (Newtonian)
viscosity lower than the two previous solutions;
10 4: Arabinogalactan non-linear trend (viscosity
lower than the three previous solutions).

The description of the graph can be further
exemplified by the following table which reports
the viscosity values (mPa.s) at 10[1/s] at a
15 fixed point corresponding to A.

Table 8 follows.

Table 8

Sample 1 Hyaluronic Acid	1.50
Eye drops 2 Hyaluronic Acid + Arabinogalactan	1.1
Sample 3 Complete eye drops A	0.97
Sample 4 Arabinogalactan	0.16

From the data obtained in table 8 it can be
20 noted that:

- Hyaluronic acid alone has a higher viscosity
(1.50 mPa.s) than the viscosity of hyaluronic

acid + arabinogalactan (1.1 mPa.s): in fact,
there is a decrease of 0.4 mPa.s.;

- higher than Eye Drops A (0.97 mPa.s):
in fact, there is a further decrease of 0.03
5 mPa.s. This very slight decrease could be
ascribed to the presence of Vitamin E TPGS
in the eye drops;

- Finally, even higher than the
arabinogalactan 0.16 mPa.s, which is
10 practically non-viscous.

CONCLUSIONS

In conclusion, with the tests carried out, the
inventors demonstrated for the first time that the
association between arabinogalactan and hyaluronic acid
15 has a synergistic effect in the reduction/inhibition of
uric acid by the enzyme xanthine oxidase. The
synergistic effect of the AG + HA association,
demonstrated by the experimental part, is statistically
significant and the inhibiting effect thereof is
20 greater than that expected from the mere algebraic sum
of the effects obtained for the same compounds alone.

Similarly, the same synergistic phenomenon of the
AG + HA association has been observed and demonstrated
in the ability to reduce superoxide anion formation.
25 Also in this case the synergistic effect of the AG + HA
association is statistically significant and is greater
than that obtained by the algebraic sum of
arabinogalactan and hyaluronic acid alone.

These innovative results not deducible from the
30 state of the art are the backbone of the object of the

present invention, i.e., a formulation of an ophthalmic composition comprising hyaluronic acid and arabinogalactan, with the addition of panthenol, vitamin E-TGPS and trehalose, for use in the treatment
5 of dry-eye syndrome. The synergistic effects of the AG + HA association, synergy even maintained in the testing of the ophthalmic composition in the entirety thereof, integrates the treatment of dry-eye syndrome, also and above all (if) accompanied by inflammatory
10 phenomena, which are often connected thereto. In fact, the action of the AG + HA association, both of inhibiting uric acid formation by xanthine oxidase, and the inhibition of superoxide anion formation, are strong indications of an anti-inflammatory power.

15 In particular, xanthine oxidase plays a key role in inflammatory processes, especially those associated with dry-eye syndrome; moreover, the inhibiting capacity of the superoxide anion, by the AG + HA association and by the formulation of the ophthalmic
20 composition of the invention, is of particular importance to eliminate all those phenomena of cytotoxicity, associated with the superoxide anion, and origin of the inflammatory state of the ocular surface.

Finally, the uniqueness and innovation of the AG +
25 HA association, and consequently of the formulation of the ophthalmic composition based on this association and of the present invention, have been independently confirmed in parallel also by the rheological measurements, which have shown a real interactive
30 effect between arabinogalactan and hyaluronic acid,

also maintained by the preferred ophthalmic formulation of the present invention both in the form of eye drops and gel.

5 REFERENCES

1. Histol Histopathol (2002) 17: 755-760 Xanthine oxidoreductase and xanthine oxidase in human cornea
2. J. ˇCejková¹, T. Ardan¹, M. Filipec² and A. Midelfart³ Curr Eye Res. 2011 Jan;36(1):21-8. doi:
10 10.3109/02713683.2010.523193. Arabinogalactan as active
10 compound in the management of corneal wounds: in vitro toxicity and in vivo investigations on rabbits.
3. Burgalassi S, Nicosia N, Monti D, Falcone G, Boldrini E, Fabiani O, Lenzi C, Pirone A, Chetoni P.
15 Larch arabinogalactan for dry eye protection and treatment of corneal lesions: investigations in rabbits. J Ocul Pharmacol Ther. 2007 Dec;23(6):541-50.
4. Rolando M¹, Valente C. Establishing the tolerability and performance of tamarind seed polysaccharide (TSP)
20 in treating dry eye syndrome: results of a clinical study. Ophthalmol. 2007 Mar 29;7:5.
5. Islam Mahmoud Hamdi. Effect of D-Panthenol on Corneal Epithelial Healing after Surface Laser Ablation. Journal of Ophthalmology. Volume 2018,
25 Article ID 6537413, 6 page
6. Ming Tang,^a Alan J. Waring,^b and Mei Hong^a. Trehalose-Protected Lipid Membranes for Determining

Membrane Protein Structure and Insertion. J Magn Reson. 2007 Feb; 184(2): 222-227.

7. Jinyang Li, Christophe Roubeix, Yu Wang, Shuai Shi, Guoting Liu, Christophe Baudouin, Wei Chen
5 Therapeutic efficacy of trehalose eye drops for treatment of murine dry eye induced by an intelligently controlled environmental system. Molecular Vision 2012 16 317-329
8. Christophe Baudouin, Murat Irkeç, Elisabeth M. Messmer, José M. Benítez del Castillo, Stefano Bonini
10 Clinical impact of inflammation in dry eye disease: proceedings of the ODISSEY group meeting. Acta Ophthalmol. 2018 Mar; 96(2): 111-119.
9. Jayesh Vazirani Ocular surface inflammation in dry
15 eye disease: What we know and what we do not. Indian J Ophthalmol. 2018 Jan; 66(1): 44.
10. Yagci A1, Gurdal C. The role and treatment of inflammation in dry eye disease. Int Ophthalmol. 2014 Dec; 34(6):1291-301. doi: 10.1007/s10792-014-9969-x.
20 Epub 2014 Jul 26.
11. Cejková J1, Ardan T, Jirsová K, Jechová G, Malec J, Simonová Z, Cejka C, Filipec M, Dotrelová D, Brunová B. The role of conjunctival epithelial cell xanthine oxidoreductase/xanthine oxidase in oxidative reactions
25 on the ocular surface of dry eye patients with Sjögren's syndrome. Histol Histopathol. 2007 Sep; 22(9):997-1003. doi: 10.14670/HH-22.997

12. P Kuppusamy and J L Zweier.Characterization of free radical generation by xanthine oxidase. Evidence for hydroxyl radical generation. The Journal of Biological Chemistry 264, 9880-9884. June 15, 1989
- 5 13. Theodore W. & Raymond Petrillo and Thomas Jefferson
nSuperoxide anion radical as an indirect mediator in
ocular inflammatory disease. Journal Current Eye
Research Volume 3, 1984 - Issue 1 243-252
14. Carolina Pustovrh, Alicia Jawerbaum, Debora Sinner,
10 Mario Pesaresi, Mario Baier, Paula Micone, Martha
Gimeno and Elida T. Gonzalez. Membrane-type matrix
metalloproteinase-9 activity in placental tissue from
patients with pre-existing and gestational diabetes
mellitus.Reproduction, Fertility and Development 12(6)
15 269 - 275 2000
15. Owen PL1, Johns T Xanthine oxidase inhibitory
activity of northeastern North American plant remedies
used for gout. J Ethnopharmacol. 1999 Feb;64(2):149-60.
16. Massey,V: Handbook of Methods for oxygen radical
20 Research Third Edition 1987 p. 213-2015 Irwin
Fridovich. Biochem.Biophys.Acta 34,255.1959
- 17) Biochem Pharmacol. 1990 May 15;39(10):1597-601.
Comparative evaluation of the antioxidant activity of
alpha-tocopherol, alpha-tocopherol polyethylene glycol
25 1000 succinate and alpha-tocopherol succinate in
isolated hepatocytes and liver microsomal suspensions.
Carini R1, Poli G, Dianzani MU, Maddix SP, Slater TF,
Cheeseman KH.

• Author information

Department of Experimental Medicine and Oncology,
University of Turin, Italy.

* **Abstract**

5 The antioxidant activity of alpha-tocopherol
polyethylene glycol 1000 succinate (TPGS) and of
alpha-tocopherol succinate (TS) has been examined in
isolated hepatocytes and microsomal fractions from
rat liver. Both TPGS and TS require esterase activity
10 to yield free alpha-tocopherol and, hence,
antioxidant activity. TPGS and TS consistently
exerted a more effective antioxidant protection than
an equivalent amount of directly-added free alpha-
tocopherol. The low antioxidant efficiency of
15 directly added free alpha-tocopherol in such water-
based experimental systems as used here seems to be
due to its extreme hydrophobicity. TPGS, on the other
hand, is an extremely hydrophilic compound which is
being examined as a useful source of alpha-tocopherol
20 in certain clinical situations and is here shown to
be a convenient and effective source for experimental
studies into lipid peroxidation and antioxidant
mechanisms.

CLAIMS

- 1) An ophthalmic composition comprising hyaluronic acid and arabinogalactan in synergistic amounts for use in the treatment of dry-eye syndrome.
- 5 2) An ophthalmic composition comprising hyaluronic acid and arabinogalactan in synergistic amounts according to claim 1, for use in the treatment of dry-eye syndrome, accompanied by the inflammatory phenomena related to the action of the enzyme system xanthine
10 dehydrogenase/xanthine oxidase, which are reduced due to the combined and synergistic action of the two active ingredients hyaluronic acid and arabinogalactan.
- 3) An ophthalmic composition according to claim 1 or 2, further comprising panthenol, trehalose and vitamin
15 E-D- α -polyethylene glycol (TGPS), for use in the treatment of dry-eye syndrome, accompanied by the inflammatory phenomena related to the action of the enzyme system xanthine dehydrogenase/xanthine oxidase.
- 4) An ophthalmic composition according to any one of
20 claims 1 to 3, characterized in that the hyaluronic acid amount ranges from 0.15% to 0.4% by weight, on the total weight.
- 5) An ophthalmic composition according to any one of claims 1 to 3, characterized in that the
25 arabinogalactan amount ranges from 0.40% to 1.00% by weight, on the total weight.
- 6) An ophthalmic composition according to claim 3, characterized in that the panthenol amount ranges from 0.30% to 0.60% by weight, on the total weight.
- 30 7) An ophthalmic composition according to claim 3,

characterized in that the trehalose amount ranges from 3.00% to 4.00% by weight, on the total weight.

8) An ophthalmic composition according to claim 3, characterized in that the vitamin E-D- α -polyethylene glycol (TGPS) amount is comprised between 0.030% to 0.050% by weight, on the total weight.

9) An ophthalmic composition according to claim 3, characterized in that it is filterable and sterilizable at 0.2 microns.

10) An ophthalmic composition according to claim 1 or 3, further comprising one or more additional therapeutic agents, selected from the group comprising growth factors, anti-inflammatory agents, vitamins, fibronectin and collagen, amino acids and/or pharmacologically acceptable substances for the treatment of dry-eye syndrome, accompanied by the inflammatory phenomena related to the action of the enzyme system xanthine dehydrogenase/xanthine oxidase.

11) An ophthalmic composition according to claim 3, further comprising a gelling agent such as Poloxamer 407, in a range of concentrations between 1% and 9% by weight.

12) Use of a hyaluronic acid and arabinogalactan association, in synergistic amounts, for preparing, after sterilization by filtration, an ophthalmic product for topical use in the form of eye drops for the treatment of dry-eye syndrome.

13) Use of a composition comprising a hyaluronic acid and arabinogalactan association, further comprising panthenol, trehalose, and vitamin E-D- α -polyethylene

glycol (TGPS), for producing eye drops for the treatment of dry-eye syndrome, after sterilization by filtration.

14) Use of a composition comprising a hyaluronic acid
5 and arabinogalactan association, further comprising panthenol, trehalose, and vitamin E-D- α -polyethylene glycol (TGPS), with the addition of a gelling agent, such as Poloxamer 407, for producing a gel for the treatment of dry-eye syndrome.

10 15) Use of a composition comprising hyaluronic acid, arabinogalactan, panthenol, trehalose and vitamin E-D- α -polyethylene glycol (TGPS), for preparing eye drops or a gel for the treatment of dry-eye syndrome, accompanied by the inflammatory phenomena related to
15 the action of the enzyme system xanthine dehydrogenase/xanthine oxidase.