Zonaker® T

Hialuronato de Sodio 0.2%, TS-Polisacárido 0.2%

LA CIENCIA DE LO

natural

EN BENEFICIO DEL PACIENTE CON OJO SECO

Laboratorios Grin®
A LUPIN GROUP COMPANY

En 2014, Laboratorios Grin® se une a Lupin Limited

Fundada en 1955 como una empresa mexicana.

Con el objetivo de elaborar medicamentos oftalmológicos con estándares de la más alta calidad.

2º referente en el mercado **oftalmológico en México.** (Unidades)

Investigación, desarrollo, producción y distribución **a nivel mundial.**

Contamos con más de **450 colaboradores.**

102 PRODUCTOS en las áreas de oftalmología y atención primaria.

12MM de dólares Invertidos en la planta manufactura aprobada por autoridades de salud en México.

Exportamos nuestros productos a **Haití, República Dominicana, Honduras, Guatemala, El Salvador, Perú y Panamá.**

Con sede en Mumbai, India.

Lupin Limited es una empresa farmacéutica transnacional, que desarrolla una amplia gama de productos de biotecnología y API's a nivel mundial.

CEO
Vinita D. Gupta.
"Lupin es una compañía muy profesional, mi meta es llevar el negocio al siguiente nivel".

Orientada a la innovación, producción y desarrollo de una amplia gama de principios activos y farmacéuticos, así como formulaciones genéricas y de marca.

Presencia en **más de 100 países** y más de **16,000 empleados** a nivel mundial.

Lupin es la **2ª compañía farmacéutica en India** y la 6ª a nivel mundial de genéricos.

Tiene **más de 18 instalaciones** configuradas para cumplir con estrictos estándares de calidad **para investigación y manufactura.**

Con 10 años de experiencia en Europa, llega a México una fórmula sinérgica, **única**[1], **innovadora y natural.**[2]

TSP* 0.2% + **HS** 0.2%**

Estructura **similar a la glicoproteína mucínica (MUC1)**[2-5]

Propiedades **mucomiméticas y mucoadhesivas**[2-4,6]

Retiene e incorpora grandes volúmenes de agua[2-5]

Favorece la **reepitelización de la córnea**[3]

Mayor hidratación
Mayor tiempo de retención[2-5]

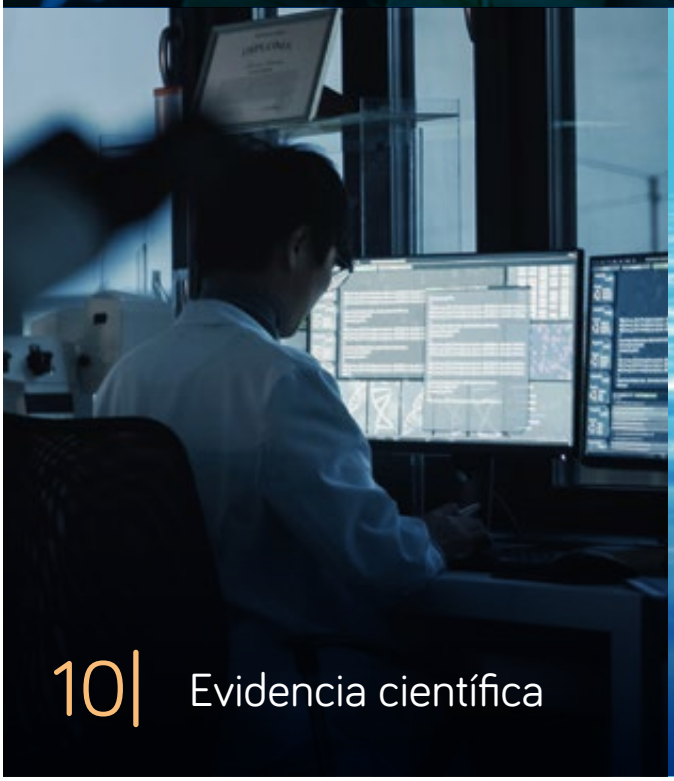
ALIVIO PROLONGADO

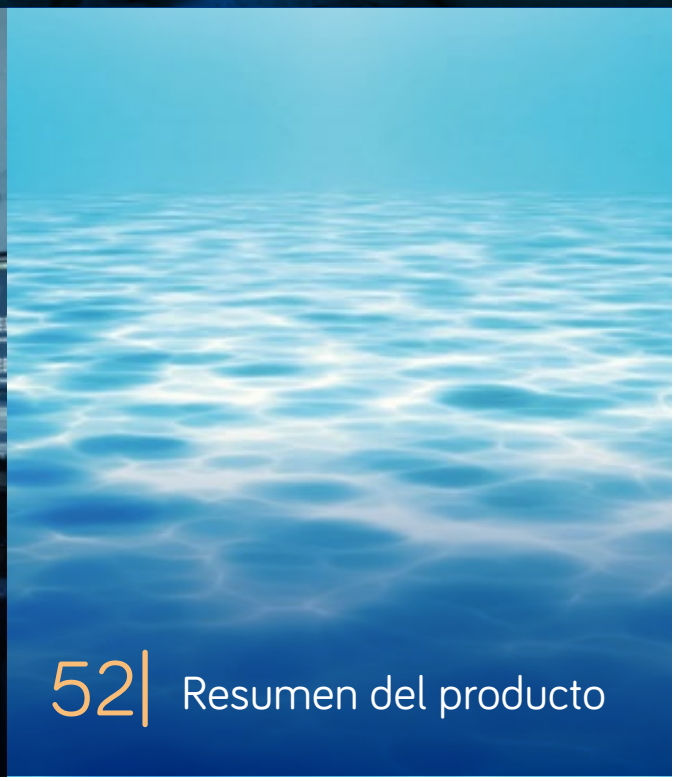
MEJOR CALIDAD DE VIDA PARA LOS PACIENTES DE OJO SECO[6]

*TSP: Polisacárido de la semilla de tamarindo, por sus siglas en inglés
**HS: Hialuronato de sodio

Zonaker® T
Hialuronato de Sodio 0,2%, TS-Polisacárido 0,2%

ÍNDICE





HISTORIA Y CRONOLOGÍA DEL PRODUCTO

Zonaker® T
Hialuronato de Sodio 0,2%, TS-Polisacárido 0,2%

¡Ahora en México!

Producto importado de Italia

La ciencia de lo natural en beneficio del paciente con ojo seco

1990

Farmigea, nuestro socio estratégico, y la Universidad de Pisa en Italia **iniciaron estudios del extracto de Semilla de Tamarindo.**

1996 2005

Se **obtuvo la patente** y la autorización de uso para el Polisacárido de Semilla de Tamarindo en **uso oftálmico.**

2001 2005

Se estableció al Polisacárido de Semilla de Tamarindo (TSP por sus siglas en inglés) como componente adecuado para desarrollo clínico.

2001

Se lanza al mercado Europeo con conservador.

2012

Se lanza al mercado Europeo la **fórmula mejorada SIN CONSERVADOR.**

2022

Hoy con 10 años de experiencia en pacientes europeos, llega a México Zonaker®T, a través de la colaboración de Laboratorios Grin® y Farmigea.

INSTRUCTIVO ZONAKER®T

PROYECTO DE INSTRUCTIVO ANEXO: INFORMACIÓN PARA EL USUARIO

Solución Lubricante Oftálmica.
Hialuronato de Sodio 0.2%, TS-Polisacárido 0.2%

Lea todo el instructivo antes de usar el producto, ya que contiene información importante para usted.

- Conserve este instructivo. Puede que lo tenga que leer nuevamente en el futuro.
- Si presenta efectos secundarios, notifique los incidentes adversos al correo: farmacovigilancia@lgrin.com. Esto incluye cualquier posible efecto secundario.

¿Qué incluye este instructivo?

1. ¿Qué es Zonaker® T y para qué se utiliza?

Es una solución oftálmica estéril, hidratante y lubricante, sin conservantes, que contiene sustancias funcionales que normalizan y protegen la superficie del ojo: Hialuronato de Sodio (mucomimético lubricante) y TS-Polisacárido (protector y equilibrante). Sin conservadores y sin fosfatos.

Zonaker® T proporciona lubricación y alivio de larga duración a la sequedad en los ojos provocada por elementos ambientales (viento, sol, agua salada, humo, aire acondicionado, calefacción), uso excesivo de computadora o factores mecánicos (cirugía ocular, uso de lentes de contacto) protegiendo la córnea y la conjuntiva gracias a la sinergia de ambos componentes.

El Ácido Hialurónico es una sustancia que origina soluciones mucomiméticas con óptimas propiedades lubricantes; dichas soluciones tienen una viscosidad tal que garantizan un efecto humectante y estabilizador de la película lagrimal.

El TS-Polisacárido es una sustancia natural extraída de las semillas de la planta *Tamarindus indica*, útil para la protección de la superficie córneo-conjuntival. El TS-Polisacárido forma una película protectora que ayuda a recuperar el equilibrio natural de la película lagrimal y la superficie ocular.

La combinación de las dos sustancias permite, por tanto, una actividad sinérgica de normalización de la superficie córneo-conjuntival que está protegida contra las irritaciones debidas a causas físicas-ambientales (viento, sol, humo, aire seco), a un estrés visual (uso excesivo de luz, uso Intensivo de aparatos electrónicos) o a factores mecánicos (lentes de contacto, cirugía ocular), ofreciendo un alivio duradero.

Debido a que el producto carece de conservadores, es aconsejable para ojos sensibles, para uso frecuente y prolongado y para usuarios de lentes de contacto.

Precauciones y advertencias:

- No use **Zonaker® T** en caso de sensibilidad a cualquiera de los componentes de la fórmula.
- Después de la administración, en algunos casos, puede presentarse visión borrosa temporal debido a la viscosidad de la solución. Por lo tanto, se recomienda esperar hasta que la visión borrosa desaparezca antes de realizar cualquier actividad que requiera precisión visual.
- No se garantiza la esterilidad del producto en caso de que el empaque primario tenga señales de haber sufrido ruptura previa.

2. ¿Cómo debe usar Zonaker® T?

- Este producto es para uso exclusivo oftálmico externo. No debe ingerirse.

- Debe aplicar una gota en cada ojo, varias veces al día, según sea necesario.
- No permita que la punta del frasco toque el ojo o las áreas alrededor de los ojos. La solución puede contaminarse con bacterias que podrían causar infecciones oftálmicas, lo que pudiera causar un daño severo en el ojo, incluyendo la pérdida de la visión. Para evitar la posible contaminación del contenedor, mantenga la punta de éste lejos de cualquier superficie.
- Si usted está utilizando **Zonaker® T** junto con otras gotas para los ojos, éstas se deberán aplicar con 10 minutos de diferencia.

Instrucciones de uso:

Antes de la aplicación de las gotas:

- Lave sus manos antes de abrir el frasco.
- No utilizar este producto si nota que el sello de seguridad del frasco se encuentra roto antes de utilizarlo por primera vez.

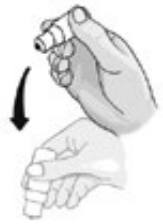
Aplicación de la solución:

1. Sostenga el frasco por debajo de la tapa y abra el frasco desenroscando la tapa. Evite tocar con la punta cualquier superficie para evitar la contaminación de la solución.

2. Sostenga el frasco boca abajo y apriete suavemente el fondo del frasco para soltar una gota del producto, en la superficie de su ojo, a la vez.

3. Repita lo mismo para aplicar el producto en el otro ojo, si fuera necesario.

4. Cierre cuidadosamente el frasco después de cada uso, comprobando que no queden gotas residuales en la boquilla. En caso de que quedara líquido en la boquilla, sacuda el frasco con un movimiento rápido de la muñeca para eliminarlo.



3. ¿Cómo almacenar Zonaker® T?

- Almacene este producto fuera del alcance de los niños. Después de abierto el frasco, el producto puede ser utilizado durante un máximo de 90 días.
- No utilice este producto después de la fecha de caducidad indicada en el envase.
- Asegúrese que el frasco esté bien cerrado y consérvelo a no más de 25°C.
- No utilice este producto si observa que el sello de garantía está roto al usar por primera vez el envase.

4. Contenido de la caja e información adicional

¿Qué contiene **Zonaker® T**?

Fórmula: Cada mL contiene:

Hialuronato de sodio	2.0 mg
TS-Polisacárido	2.0 mg
Vehículo cbp	1.0 mL

Se presenta en forma de solución oftálmica, se puede encontrar en las siguientes presentaciones:

- Caja con frasco con 10 mL
- Caja con frasco con 10 mL (original de obsequio)
- Caja con frasco con 5 mL (muestra de obsequio)

EVIDENCIA CIENTÍFICA

European Scientific Journal September 2015 edition vol.11, No.27 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

NATURAL POLYMER OF TAMARIND SEED: A PROSPECTIVE CARRIER FOR OCULAR DRUG DELIVERY

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Abstract

Natural polysaccharide-based biomaterials are currently being explored as novel drug delivery devices. Important properties of the polysaccharides include controlled biological activity and biodegradability. The tamarind seed is a by-product of the tamarind industry. The decorticated flour, known as tamarind kernel powder has been tried for various biomedical applications such as drug delivery carriers. The xyloglucan component of it, a hemicellulose, was found to be a biocompatible, non-toxic and cheap agro-based material that could be used safely for controlled drug delivery systems. Studies with tamarind-seed polysaccharide nanocomposites have been conducted, where tamarind and polyvinyl alcohol were blended with Cloisite 30B solution in different ratios showing a sustained delivery of drugs. We certainly foresee the prospect of bio-adhesive carriers, such as muco-adhesive polymers of tamarind-seed polysaccharides an effective solution of achieving bioavailability of various ocular drugs when used as topical preparations.

Keywords: Tamarind seed polysaccharide, xyloglucan, drug delivery, ocular

Introduction

The recent use of biopolymers derived from agricultural feed stocks has attracted the attention of many researchers for various biomedical applications (Kalia S 2011). One such cheap and agro-based biomaterial is tamarind seed polysaccharide (TSP) obtained from tamarind seed. Tamarindus indica L, is a multipurpose tropical fruit tree primarily used for its fruits which are eaten fresh or processed to be used as a seasoning or spice. The fruits and seeds can also be processed for non-food uses. Recently various biodegradable based plants and animal based products have been explored for the use as drug carriers (Sahoo R 2010, Sahoo S 2010, Sahoo S

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2011).Tamarindus indica L., commonly known as tamarind tree is one of the most important multipurpose tree species in the Indian sub-continent. It is a large evergreen tree with an exceptionally beautiful spreading crown, and is cultivated throughout almost the whole country, except in the Himalayas and western dry regions (ICFRE 1993, Rao Y S 1999). The major industrial use of the seeds is in the manufacture of TKP. It is prepared by decorticating the seed and pulverising the creamy white kernels (Khoja AK 2001).

However the medical use; especially the prospective use in drug delivery of TSP has not been reviewed extensively in literature. Therefore we wanted to have a review covering the various experimental studies those have explored the possibility of using TSP polysaccharides either through in-vitro or in vivo studies. We searched the articles published & featured in Science direct through electronic search. All the studies covering the ocular drug delivery aspects were included in review. The studies mentioning drug delivery to other parts of body were excluded from this review.

Tamarind Xyloglucan

Xyloglucan is a major structural polysaccharide in the primary cell wall of higher plants. Cell growth and enlargement are controlled by the looseness of a thin net of microfibrils made of cellulose. Xyloglucan cross-links these cellulose microfibrils and provides the flexibility necessary for them to slide. (Glicksman M 1986).

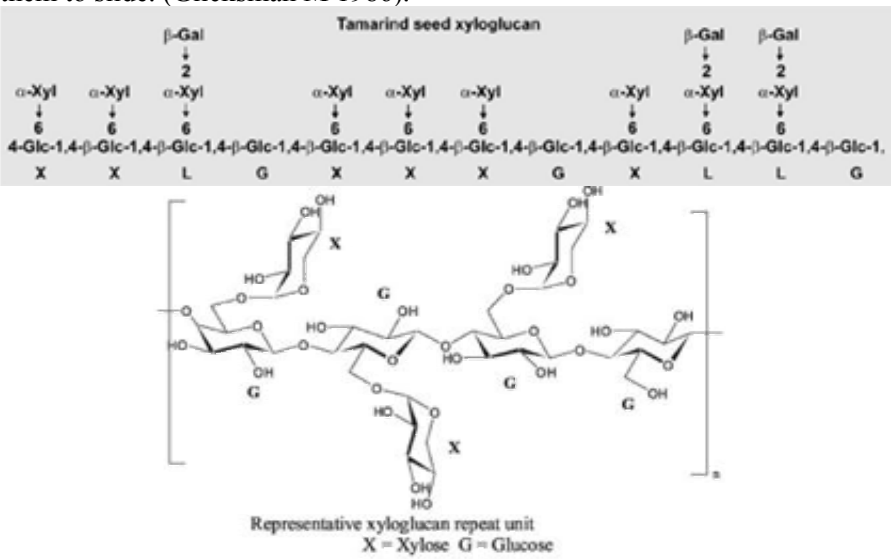

Figure.1 Biochemical Structure of Xyloglucan

Purified, refined tamarind XG is produced in Japan and is permitted as a thickening, stabilizing, and gelling agent.spaceTamarind XG has a (1→4)-β-D-glucan backbone (Figure.1) that is partially substituted at the O-6 position of its glucopyranosyl residues with α-D-xylopyranose (Gidley MJ 1991). In DSC measurements, the gelation was detected as a peak that appeared at higher temperatures than a peak arising from helix-coil transition of gellan alone . It was also detected as a change in circular dichroism which was not observed in tamarind XG alone and gellan alone .Judging from the results it was concluded that tamarind XG and gellan may associate to form a gel network (Nitta Y 2003).

Kochumalayil et al (Kochumalayil JJ 2013) oriented bionanocomposite coatings with strong in-plane orientation of clay platelets for the first time prepared by continuous water-based processing. Montmorillonite (MTM) and a "new" unmodified biological polymer XG were combined. The resulting nanocomposites were characterized by field emission SEM, transmission electron microscopy (TEM), and x-ray defraction (XRD). XG adsorption on MTM was measured by quartz crystal microbalance analysis. Mechanical and gas barrier properties were measured, also at high relative humidity. The reinforcement effects were then modeled and XG dimensions in composites estimated using atomistic simulations. The nanostructure showed highly oriented and intercalated clay platelets .

Mucoadhesive Properties of Tamarind seed polysaccharide (TSP)

Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Over the past few decades, mucosal drug delivery has received a great deal of attention. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome.TSP is a new formulation derived from the tamarind seed having mucoadhesive characterestics. The main component of tamarind seed has been identified as a non-ionic, neutral, branched polysaccharide consisting of a cellulose-like backbone that carries xylose and galactoxylose substituents (Saettone M 1997). The configuration of TSP gives the product a 'mucin-like' molecular structure, thus conferring optimal mucoadhesive properties (Mannucci LL 2000) .

Research has also shown that at the concentrations present in the ophthalmic formulations studied, TSP has an important characteristic that makes it similar to natural tears, whereby it is able to crystallise into a fern-like shape (Mannucci LL 2004). It has been suggested that the similarity of the structure of TSP to endogenous mucin may allow a formulation containing this polymer to adhere readily to the ocular surface for prolonged periods and provide sustained relief from the symptoms of dry eye

European Scientific Journal September 2015 edition vol.11, No.27 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

(Burgalassi S 1999). Indeed studies undertaken to date suggest that TSP may have some benefits over hyalurnic acid in relation to ocular retention time, wound healing properties and relief of dry eye symptoms (Mannucci LL 2000, Rolando M 2007). Overall, TSP has several physicochemical properties that make it suitable for the management of dry eye syndrome and which potentially have distinct advantages over currently available preparations.

Sahoo et al studied that the mucoadhesive polymer XG extracted from tamarind seeds could serve as a viscosity enhancer showing mucomimetic, mucoadhesive properties. The researchers described that several features make TSP an attractive candidate as a vehicle for ophthalmic medicaments for instance: (i) it is completely devoid of ocular toxicity; (ii) it has recently been put on the market as a tear fluid substitute because of its effectiveness in preventing alterations of the corneal surface for keratoconjunctivitis sicca; (iii) it increases the cornealwound healing rate; (vi) it reduces the in vitro toxicity exerted by timolol, methiolate, and fluoroquinolones on human conjunctival cells; and (v) it significantly increases the corneal accumulation and intraocular penetration of gentamicin and ofloxacin when administered topically to healthy rabbits (Sahoo S 2010).

TSP for Drug Delivery System:

Amongst all of the hydrophilic polymers, polysaccharides have become most recognised due to their widespread uses. TSP in particular, is conventionally known to bind, stabilise, thicken, suspend and emulsify agents as well as enhance viscosity. Its role in wound healing and as a carrier in novel drug delivery systems via ocular, oral, buccal, and colonic routes has also become increasingly acknowledged. In addition, TSP also has non-medical uses in nanofabrication, cosmetics and the food industry. Increasing discovery of the multiple roles of TSP has been possible due to its non-toxic nature and general acceptability by regulating authorities.

Other than the well-known uses of TSP, it has been identified to potentiate controlled release of both water soluble and water insoluble drugs. For instance, zero order release can be achieved by taking a sparingly soluble drug like indomethacin from TSP. The rate of release for these drugs can be controlled by using suitable diluents such as lactose and microcrystalline cellulose. Specific to water-soluble drugs, the release amount can also be controlled by partially cross-linking the matrix, here the degree of cross-linking can be altered thus modifying the extent of drug release (Sumathi S 2002).

Sahoo et al studied the nanocomposite of TSP in the controlled release of an anti-cancer drug, Paclitaxel (Sahoo R 2010). It was noticed that controlled delivery devices with biodegradable polymers had greater positive

European Scientific Journal September 2015 edition vol.11, No.27 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

significance over delivery systems that required surgical removal of the device. TSP as a biocompatible, non-toxic and cheap agro-based material was used safely for this controlled drug delivery system. A prolonged release of Paclitaxel was proven by use of TSP as the controlled release material. Swelling studies of the nanocomposites have also reported to be effective in releasing in a controlled manner.

Use as Ocular Drug Release Modifiers

Much research is currently in progress studying the efficacy of TSP for ocular preparations. Few studies have reported that TSP could be useful as artificial tears for the treatment of dry eye syndrome due to its mucoadhesive properties and pseudoplastic rheological behaviour (Khounvilay K 2011, Rolando M 2007). Alongside this, the high viscosity and unique mucoadhesive strength of TSP make it an ideal candidate for increasing the pre-corneal residence time for many topical ocular preparations.

The effect of an ophthalmic preparation containing 0.5% timolol (β-adrenergic blocker solution) plus 1 or 2% TSP on intraocular pressure (IOP) was evaluated in rabbits. It was concluded that timolol with TSP could be a good formulation for treating high IOP as the duration action of the formulation lasted for 12hours (D′amico M 1999). Similarly, another ocular drug pilocarpine, known to lower IOP has also been studied using tamarind gum as a novel bioadhesive material forming in situ gelling systems. The combination of alginate, tamarind gum and chitosan was identified as the most successful for sustained delivery of 80% of the drug for 12 hours. In vivo mitotic studies and ocular irritation studies have showed a significant long-lasting decrease in pupil diameter of rabbits with a well-tolerated non-irritating effect with a tamarind gum based formulation (Mehra GR 2010).

Ghelardi et al (Ghelardi E 2010) employed ocular administration of hydrophilic and hydrophobic antibiotics such as gentamicin and ofloxacin using TSP as a mucopolysaccharide. When TSP viscosified solutions of the drug were instilled into rabbits, the aqueous humour and corneal concentration of the dose was remarkably higher than the drug itself. It was also noted that the absorption and drug elimination was prolonged by use of TSP, for example, the concentration of drug in the cornea exceeded the minimum inhibitory concentration (MIC) found in cases of keratoconjunctivitis.

Other studies have postulated the effectiveness of ocular delivery of antibiotics, rufloxacin and ofloxacin with mucoadhesive polymer extracted from tamarind seed, for the treatment of bacterial keratitis experimentally induced by Pseudomonas aeruginosa and Staphylococcus aureus in rabbits. They found that the formulation significantly increased the intra-aqueous

European Scientific Journal September 2015 edition vol.11, No.27 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

penetration of the drugs in both infected and uninfected eyes. The effect of TSP on delivery of rufloxacin for a significant reduction of bacteria in the cornea was better than using rufloxacin alone. This was most probable due to the prolongation of the pre-corneal residence time subsequently increasing drug availability (Khounvilay K 2011).

In order to mask the unpleasant odour and to prevent the fast degradation of the TSP, it has been subjected to chemical modification by treatment with various groups such as acetyl, hydroxyalkyl and carboxymethyl . In a study by Kaur et al (Kaur H 2012), nanoparticles of carboxymethyl tamarind kernel polysaccharide (CMTKP) were used for ophthalmic drug delivery. TSP was carboxymethylated in order to impart an anionic nature to the polymer; this helped to increase its viscosity with an increase in shelf life and decreased biodegradability. The solubility of TSP in cold water was also enhanced. In the study nanoparticles of CMTKP loaded with tropicamide were formed by an ionotropic gelation technique. The in vitro study result of tropicamide-loaded CMTKP nanoparticles showed no significant difference in the permeation of the nanoparticles compared to that of the aqueous solution of the drug. The formulation was found to be non-irritant.

Uccello-Barretta et al (Uccello-Barretta G 2010) studied the interaction between TSP and hyaluronic acid (HA) with the aim of developing a promising excipient for ocular delivery. Nuclear Magnetic Resonance (NMR) spectroscopy was performed to determine the interaction between TSP and HA, this also helped to determine the optimum ratio of the TSP and HA in the mixture. A TSP:HA of 3:2in the mixture showed significant mucoadhesivity. An in vivo study on rabbits was also performed by the researchers, this was done by calculating the mean and maximum residence time of various TSP and HA mixtures in pre-corneal area. The results of these in vivo studies showed that the TSP:HA mixture in a 3:2 ratio showed strong mucoadhesivity compared to individual components and other mixtures. They concluded in saying that the enhanced ocular drug availability by the TSP and HA mixture was attributed to the strong mucoadhesivity. The same authors also used ketotifen fumarate (KT) for the ophthalmic dosage forms which showed more favourable affinity towards TSP rather than towards hydroxyethylcellulose (HEC) or HA. The higher affinity of TSP compared to HEC and HA was demonstrated with the use of NMR spectroscopy and this result was confirmed by a dynamic dialysis technique, which showed that the fraction of KT bound to TSP was significantly higher than that bound to HEC or HA .This proves that KT with TSP helps in stabilising the tear film, and thus prolonging the residence time of KT tear fluid. The strong mucoadhesive nature of TSP is responsible for its enhanced ocular drug availability.

Burgalassi et al (Burgalassi S 2000) carried out a study on corneal epithelium wound healing using TSP. TSP being a natural polymer helps in the adhesion of cells to laminin, thus promoting ocular wound healing. The work of these researchers on rabbits showed that TSP could help in would healing, although this was dependant on its varying concentrations.

Conclusion

This review found that multiple previous studies have shown TSP used to have strong adsorption to cellulose. In addition, the basic characteristics of tamarind seed XG have been proven to be similar to those of plant cell wall XG. Furthermore, tamarind XG has a very high molar mass making it mechanically advantageous. This biodegradable glycosaminoglycan and a galactoxyloglucan polysaccharide have been found to have a wide application in the pharmaceutical industry for controlled drug delivery. The xyloglucan component has been described as a viscosity enhancer as it is mucomimetic and mucoadhesive. For ocular drug delivery, several features make TSP an attractive candidate as a drug delivery system. As mentioned earlier it's non-toxic & mucoadhesive nature helps retaining topically applied drug for longer duration of action. One study shown the enhancement of penetration of drug to aqueous humour of eye when delivered through TSP. These dual properties like longer stay in cornea & permeability enhancer makes TSP as an ideal carrier for ocular drug delivery. Apart from its FDA approved commercial use as one of the tear substitutes , researchers have experimentally tried TSP & it's nanocomposite for topical delivery of ocular drugs like Timolol, Fluoroquinolones, Gentamycin etc.

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European Scientific Journal September 2015 edition vol.11, No.27 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431

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ORIGINAL ARTICLE

The effect of an artificial tear combining hyaluronic acid and tamarind seeds polysaccharide in patients with moderate dry eye syndrome: a new treatment for dry eye

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Purpose: *Synergistic interactions between hyaluronic acid (HA) and tamarind seed polysaccharide (TS-polysaccharide) have been demonstrated by means of nuclear magnetic resonance spectroscopy. This study was designed to investigate the potential clinical benefit of a combination of HA and TS-polysaccharide in managing dry eye disease (DED).*
Methods: *A total of 49 subjects with moderate DED, confirmed by Ocular Surface Disease Index (OSDI) questionnaire score between 10 and 25, tear break-up time (BUT) <10 seconds, or Schirmer I test <5.5 mm after 5 minutes, and lissamine green staining of the ocular surface >2 according to National Eye Institute score system, were enrolled into this multicenter, randomized, double-masked study to receive either combination of HA and TS-polysaccharide or carmellose sodium for 3 months, both instilled 4 times per day. The assessments included OSDI questionnaire, tear film stability (BUT), tear production (Schirmer I test), and corneal and conjunctival staining.*
Results: *Patients treated with HA and TS-polysaccharide showed a statistically significant improvement in the OSDI score at the end of the study compared to the baseline and control groups. The HA and TS-polysaccharide and carmellose sodium were equally effective in reducing BUT and the extent of injury assessed by corneal and conjunctival staining. Non-significant changes were recorded for Schirmer I test.*
Conclusions: *Based on the results of this clinical trial, the combination of HA and TS-polysaccharide appears to be effective in improving the symptoms of dry eye, opening new scenarios in possible treatment of the disease by combining different molecules.*

Keywords: *Carmellose sodium, Dry eye disease, Hyaluronic acid, Tamarind seeds polysaccharide, Tear substitutes*

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INTRODUCTION

Dry eye disease (DED) is one of the most frequent pathologies in ophthalmology, affecting millions of people in Western countries. On the basis of the diagnostic criteria and the population involved, the current estimates of the prevalence of DED range from 0.1% to 33% (1). The importance of dry eye is based also on its capacity to affect the quality of

life of patients by means of symptoms of pain and irritation that in the severe forms of the disease are comparable to those reported for moderate to severe angina (2), and to limit and degrade performance of common vision-related daily activities, such as reading and driving (3).

Recent advances in the comprehension of the pathophysiology of dry eye have led to significant changes in the therapeutic management of the disease. Tear substitutes, the most frequently used treatments for mild to moderate aqueous tear deficiency, are able to provide temporary improvement in symptoms of eye irritation, blurred vision, and visual contrast sensitivity (4).

Tear substitutes containing sodium hyaluronate (SH), sodium salt of hyaluronic acid (HA), are able to improve tear film stability and to delay evaporation of the aqueous component of the tear film by means of their mucomimetic properties (5), viscoelastic and rheologic behavior (6), and water-retention properties (7). Tear substitutes containing SH have demonstrated improvement of signs and symptoms of DED greater than saline (8), but also greater than tear substitutes containing carboxymethylcellulose (9) or hydroxypropyl-methylcellulose (10), both with viscoelastic properties similar to SH. Tamarind seed polysaccharide (TS-polysaccharide), a nonionic, neutral, branched polysaccharide obtained from tamarind seed, consists of a cellulose-like backbone that carries xylose and galactoxylose substituents leading to a mucin-like molecular structure, similar to transmembrane MUC1 (11), suggesting a role for sustained relief from the symptoms of DED (12).

Laboratory tests based on the employment of nuclear magnetic resonance (NMR) techniques showed that TS-polysaccharide is able to interact in solution with the HA, inducing conformational changes that mainly interest the internal glucose and galactose units of TS-polysaccharide and the acetyl groups of SH. This fact produces effect on the ability of the admixture to retain water that, for some concentration ratios, turns out to be remarkably higher and in a most stable matter than shown by the 2 polymers in nonmixed form (13). This finding and a preliminary open-label clinical trial (14) suggest that the mixture of TS-polysaccharide and HA might have a role in the treatment of DED.

MATERIALS AND METHODS

This study was a multicenter, double-masked, randomized, controlled trial conducted for 6 months. A total of 4 study centers from Italy participated in the study after approval by each ethical committee.

Forty-nine patients, of at least 18 years of age, attended the screening visit (day –7), during which demographic information, medical history, current medications, slit-lamp examination of the anterior segment of the eye, and lens abnormalities were recorded. The study included 4 follow-up visits (days 14, 28, 42, 56) and one study termination visit (day 84).

Eligible patients had a diagnosis of moderate DED confirmed by Ocular Surface Disease Index (OSDI) questionnaire (15) between 10 and 25, tear break-up time (BUT) <10 seconds or Schirmer I test <5.5 mm after 5 minutes, and lissamine green staining of the ocular surface >2 according to National Eye Institute conjunctival grading system (16, 17).

The exclusion criteria were ocular trauma, surgery, infection or inflammation within the 3 months preceding the study, concomitant ocular pathologies, eyelid, eyelash, or nasolacrimal apparatus abnormalities, use of drugs affecting tearing, ocular therapies within the month preceding the study, except for artificial tears if followed by a washout period, neurologic or dermatologic disease affecting the health of the ocular surface, and contact lens wear.

Eligible patients were randomized in a 1:1 ratio to receive a commercial mixture of TS-polysaccharide 0.2% and HA 0.2% (Xiloial monodose, Farmigea S.p.A., Pisa, Italy) or Optive monodose (Allegan Inc., Irvine, California, USA). Both Xiloial and Optive were primarily packaged in droppers from which any identification of the product was manually removed by a pharmacist and subsequently identified only with treatment number. Both the investigator and the patient were masked to the treatment assigned according to the masked nature of the study.

Eligible patients had to instill physiologic solution (NaCl 0,9% single dose, sterile) 4 times/day or more for the washout period, and after randomization were trained to self-instill Xiloial monodose or Optive monodose 4 times/day (approximately every 4 hours) during the duration of the study.

The following evaluations were conducted at each visit (days 14, 28, 42, 56, 84): OSDI questionnaire, BUT, ocular protection index (OPI), defined as the ratio between BUT and the interblink interval (18), Schirmer I test, and corneal and conjunctival lissamine green staining. A global efficacy assessment was performed both by the patients and the

investigator at the end of the study. As regards safety assessment, a tolerability questionnaire was administered to the patients at each visit, and all adverse events were recorded by investigators.

Statistical methods

As regards the primary and secondary endpoints (OSDI questionnaire, BUT, OPI, and Schirmer I test), the data recorded throughout the study were analyzed by analysis of variance (ANOVA) test for repeated measurements. Changes on OSDI evaluation and global efficacy assessment were analyzed by Fisher exact test. Safety data were summarized by treatment group using descriptive statistics and treatment groups compared by using a chi-square or Fisher exact test as appropriate. p Values lower than 0.05 were considered statistically significant.

RESULTS

A total of 49 patients were screened and 48 were randomized to either Xiloial (n = 23) or Optive (n = 25) and completed the study according to the protocol. Table I reports the characteristics of the patients at the randomization visit. No difference was found between the 2 treatment groups.

The OSDI value showed a significant decrease during the study in both treatment groups (ANOVA, p<0.0001), but the mean decrease reported at the end of the study was almost twice in the Xiloial group with respect to the Optive group (–14.8 vs –7.9, Xiloial and Optive, respectively). A significant increase of BUT values was obtained during the study in both groups. No significant changes were recorded for Schirmer I test values and OPI.

Figure 1 shows a significant decrease in total score of the extent of injury assessed by corneal and conjunctival staining during the study period (ANOVA, p<0.0001). In particular, the mean decreases of the total score between randomization visit and day 84 were –5.2 (±2.7) in the Xiloial group and –4.8 (±2.8) in the Optive group, without significant difference between treatments.

As regards secondary efficacy parameters, changes in the investigator's assessment of the severity of DED are shown in Figure 2. At the end of the study (day 84), the difference between the 2 treatment groups was found to be statistically significant (Fisher exact test p = 0.02).

TABLE I - CHARACTERISTICS OF THE PATIENTS AT BASELINE (RANDOMIZATION VISIT)

	HA and TS-polysaccharide (n = 23)	Carmellose sodium (n = 25)
Sex, M/F	9/14	6/19
Age, y, mean ± SD	52.2 ± 14.9	57.1 ± 17.4
BMI, mean ± SD	24.8 ± 4.6	24.3 ± 4.9
Smokers, n	4	5
Years from first DED diagnosis ± SD	4.6 ± 5.0	4.2 ± 4.6
Previous eye surgery, n	2	5
OSDI, value, ± SD	38.1 ± 11.0	39.3 ± 11.6
Break-up time, s, ± SD	4.3 ± 1.4	4.1 ± 1.4
Ocular protection index, <1/>1	16/7	17/8
Schirmer test, mm/5 min, ± SD	4.7 ± 4.2	6.2 ± 6.8
Mean ± SD intraocular pressure, mm Hg	14.9 ± 1.7	14.8 ± 1.8

BMI = body mass index (kg/m); DED = dry eye disease; HA = hyaluronic acid; OSDI = ocular surface disease index; TS-polysaccharide = tamarind seed polysaccharide.

Concerning the patient's final self-assessment of the symptoms, as reported in Figure 3, 22 out of 23 patients (95.7%) in the Xiloial group and 20 out of 25 (80.0%) in the Optive group evaluated the symptoms as "disappeared" or "improved" (Fisher exact test p = 0.19). Consistently, as shown in Figure 4, the investigators evaluated in 20 out of 23 patients (87.0%) in the Xiloial group and in 17 out of 25 (68.0%) in the Optive group the signs and symptoms as "disappeared" or "definitely improved" or "improved."

Both monodose treatments were demonstrated to be safe and well-tolerated after an exposition of 4 instillations per day for 84 days.

DISCUSSION

This is the first study to examine the effect of an artificial tear containing a new formulation of sodium hyaluronate and TS-polysaccharide (*Tamarindus indica* seed polysaccharide) named Xiloial. Our results show that in moderate dry eyes

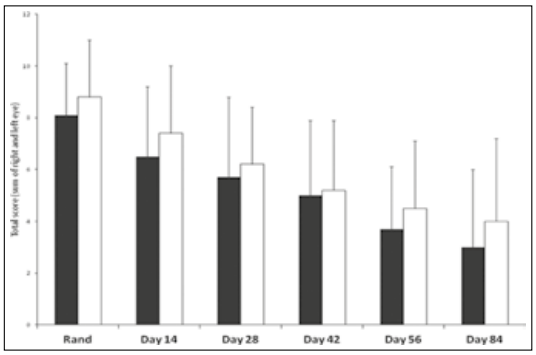

Fig. 1 - *Corneal and conjunctival staining total score. Black bars: hyaluronic acid and tamarind seed polysaccharide (Xiloial®, n = 23); white bars: carmellose sodium (Optive®, n = 25).*

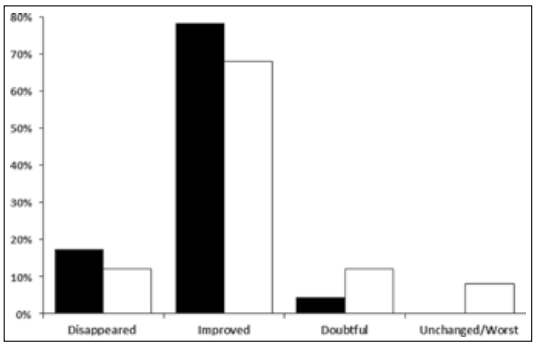

Fig. 3 - *Percentage of patients' symptoms final self-assessment. Black bars: hyaluronic acid and tamarind seed polysaccharide (Xiloial®, n = 23); white bars: carmellose sodium (Optive®, n = 25).*

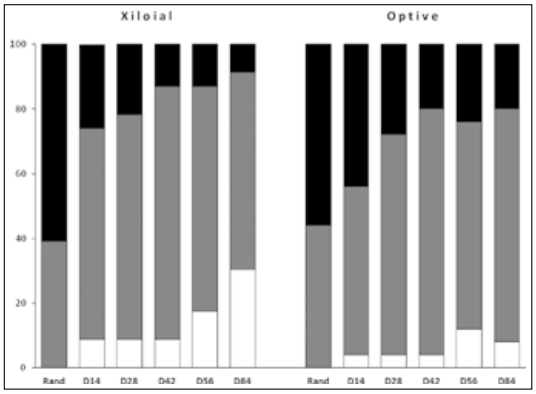

Fig. 2 - *Percentage of normal (white bars), mild (gray bars), and moderate (black bars) dry eye according to the investigators' assessment in hyaluronic acid and tamarind seed polysaccharide (Xiloial®, n = 23) and carmellose sodium (Optive®, n = 25) groups during the study visits.*

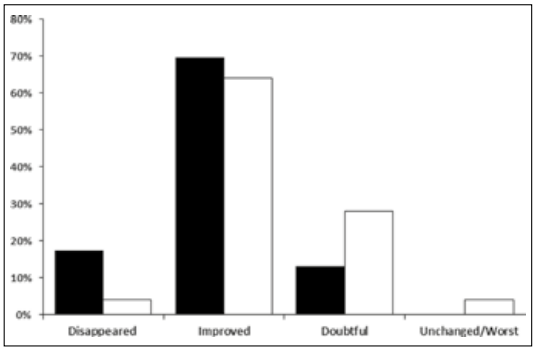

Fig. 4 - *Investigators' final global assessment of signs and symptoms. Black bars: hyaluronic acid and tamarind seed polysaccharide (Xiloial®, n = 23); white bars: carmellose sodium (Optive®, n = 25).*

Xiloial is as effective at reducing corneal and conjunctival staining as Optive, an artificial tear containing carmellose sodium, which previously was demonstrated to be effective in treating dry eye (19). Furthermore, our study showed that after 3 months of treatment symptom improvement in the Xiloial group was statistically significant.

TS-polysaccharide has found a valid use as a component of tear substitutes, having documented mucomimetic properties, such as ability to give, by evaporation, crystalline products with ferning-like morphology similar to that of crystallized tear mucus (20) and ability to remain on the ocular surface for a long time and to self-integrate with the surface of the epithelia, exerting a protective role over them (21).

The HA is chemically definable as an unbranched glycosaminoglycan, consisting of alternate units of D-glucuronic acid and *N*-acetyl-D-glucosamine, which, being completely ionized, confers high polarity to the HA molecule and consequently high solubility in water. By virtue of its good ability of linking both with water and with the epithelium cell wall, HA or its sodium salt are used as the main component in many tear substitutes in DED treatment (22).

Laboratory tests based on the employment of NMR techniques showed that TS-polysaccharide is able to interact in solution with the HA, reaching a very complex and still

not completely investigated tridimensional structure, within which water is incorporated. The water content, the type of interaction that occurs between water and the polymer materials, as well as the water distribution internally to the polymer itself have a critical influence on the mechanical properties and the muco-adhesivity and are at the base of the high degree of biocompatibility (23).

Moreover, using an *in vitro* dry eye model on human corneal epithelium, it has been demonstrated that Xiloial is able to increase within 24 hours the surface expression of mucin-4 (24) that has *in vivo* lubricating and clearing function to corneal and conjunctival epithelia (25).

This dry eye model is the first 3D experimental dry eye evaluation *in vitro* based on polycarbonated matrix where immortalized human corneal epithelium growths simulated the DED. This effect is greater than with TS-polysaccharide or HA alone and also greater than with carmellose sodium. These findings suggest that TS-polysaccharide-HA noncovalent interaction might have synergistic improved properties over those of the polymers alone.

Finally, using the described *in vitro* dry eye human model, it also has been demonstrated that HA and TS-polysaccharide, but not carmellose sodium or dexamethasone, is able to restore the histologic morphology and the microvilli density of the corneal epithelium (24).

Even if the improvements of signs and symptoms of dry eye are statistically significant in both study groups, the treatment with HA and TS-polysaccharide is associated with slightly more evident effects on the injuries assessed by corneal and conjunctival staining (–5.2 vs –4.8) and with a much more evident effect on the decrease of OSDI (–14.8 vs –7.9), very close to the level of statistical significance in spite of the very small sample size of this study. Considering the patients who responded at the end of the study to the treatments (18 and 11, in the HA and TS-polysaccharide and carmellose sodium groups, respectively), the improvement from baseline was significantly greater than in the control group ($p = 0.02$).

Further clinical studies are necessary to evaluate the effect of the new formulation of HA and TS-polysaccharide, but the combination of the 2 molecules seems to be effective in restoring the tear film and in improving ocular surface damage in patients with dry eye.

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Establishing the tolerability and performance of tamarind seed polysaccharide (TSP) in treating dry eye syndrome: results of a clinical study

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Abstract

Background: One of the problems arising from available preparations for dry eye syndrome is the limited residence time of products on the ocular surface. In this paper, we look at an innovative new treatment for dry eye, tamarind seed polysaccharide (TSP). TSP possesses mucomimetic, mucoadhesive and pseudoplastic properties. The 'mucin-like' molecular structure of TSP is similar to corneal and conjunctival mucin 1 (MUC1), a transmembrane glycoprotein thought to play an essential role in protecting and wetting the corneal surface and may explain its increased retention on the eye surface.

Methods: The activity of TSP and hyaluronic acid (HA) in the treatment of dry eye syndrome was compared in an open-label, randomised, single-centre clinical study. Thirty patients were randomised to receive three or more applications per day of either TSP 0.5%, TSP 1% or HA 0.2% (Hyalistil™) over a period of 90 days. The primary objective of tolerability was assessed by visual analogue scale (VAS), scoring of specific symptoms and the incidence of adverse events. Secondary objectives included improvement in stability of the precorneal tear film, subjective symptoms and corneal and conjunctival staining.

Results: TSP 0.5% and 1% were comparable to HA 0.2% with regard to both primary and secondary objective parameters.

TSP 1% showed benefits over HA 0.2% for the subjective symptoms; trouble blinking, ocular burning and foreign body sensation.

Conclusion: This study suggests that TSP 0.5% and 1% offer at least equivalent relief to HA 0.2% for dry eye syndrome. All treatments demonstrated optimal tolerability and are suitable for frequent use in the therapy of dry eye.

TSP 1% produced promising results in terms of improvements in certain patient symptoms and suggests benefits of the TSP formulation. This study paves the way for a larger study to further establish the performance and safety of TSP compared with HA and highlights the need to expand this therapeutic agent to a wider dry eye population.

Background

Dry eye symptoms are most commonly treated with eye drops, the major component of which is usually a viscosity-enhancing polymer. Such formulations are designed to act on the mucus and aqueous layers of the tear film, replacing lost moisture and stabilising the tear film. An issue with currently available preparations is their limited residence time on the ocular surface. In this paper, we look at an innovative new treatment for dry eye, tamarind seed polysaccharide. It is thought that the increased retention time observed with TSP on the ocular surface can be explained by similarity of the structure of TSP to transmembrane mucins, such as MUC1.

Goblet cells and lacrimal glands synthesise a spectrum of mucins that are involved in the pathophysiological events that occur at the ocular surface [1]. In the tear film, a mucus gel anchors itself and, therefore, the tear film, to the ocular surface via physicochemical interactions [2,3]. The integrity of this mucus gel, together with all the layers of the tear film, is responsible for the maintenance of normal vision and ocular comfort.

Effective distribution of the tear film across the ocular surface occurs via blinking. The healthy corneal epithelium is wettable by itself because of its ability to produce and maintain the transmembrane glycoprotein layer (MUC1). MUC1 is a membrane spanning mucin, expressed by the stratified epithelium of the conjunctiva and is believed to facilitate the spread of gel-forming mucin. Mucins possess surface activity and, in physiological concentrations, the presence of the mucin layer in the tear film converts the corneal epithelium from a hydrophobic to a hydrophilic surface so that the tear film can be spread over the cornea. If the production of mucus is reduced (for example, due to goblet cell damage, age or hormonal status), [1] mucus distribution over the preocular surface is impaired, leading to poor contact of the tear film with the eye surface and a loss of film stability [4].

Figure 1 shows the location and extent of epithelial mucins on the ocular surface in a healthy eye compared with a severe dry eye. The last ten years have seen remarkable progress in understanding the structure and character of mucins [5]. Recent application of molecular techniques has demonstrated 14 human mucin genes, e.g. MUC1 and MUC5. Of these, the mucins are now classified into gel-forming or secreting, (e.g., MUC5), soluble, (e.g., MUC7), and transmembrane, (e.g., MUC1). Gel-forming mucins are responsible for the rheological properties of mucus, whereas transmembrane mucins form a dense barrier in the glycocalyx at the epithelial tear film interface. In healthy tear film, transmembrane-spanning mucins of the glycocalyx provide a negatively charged, hydrated, epithelial cell surface which supports and facilitates spreading of the hydrated tear film – a mucous gel – with its associated defence molecules. With loss of tear volume, lipid layer, glycocalyx mucins and/or gel forming mucins, dry spots develop on the eye, leading to keratinisation and loss of mucin gene expression by the epithelial cells. It is hypothesised that loss or alteration of the membrane-spanning mucins alone or in combination with MUC5AC-secreted mucin induces dry spot formation [6].

On the ocular surface, epithelial mucins serve as:

• Pre-ocular tear film stabilisers to prevent dehydration of the underlying epithelium

• A barrier against pathogen penetration

• Wetting and lubricant agents of the cornea and conjunctiva during blinking

• Promoters of adhesion between tear film layers through hydrogen bonding

Table 1 shows the characteristics of mucin-deficient dry eye.

TSP formulation

TSP is a new formulation derived from the tamarind seed. The main component of tamarind seed has been identified as a non-ionic, neutral, branched polysaccharide consisting of a cellulose-like backbone that carries xylose and galactoxylose substituents, [7] chemical residues similar to those of MUC1. The configuration of TSP gives the product a 'mucin-like' molecular structure, [8] with particular similarity to MUC1 (Figure 2), thus conferring optimal mucoadhesive properties.

Research has also shown that, at the concentrations present in the ophthalmic formulations studied, TSP has an important characteristic that makes it similar to natural tears, i.e. its ability to crystallise in a fern-like shape [9].

It has been suggested that the similarity of the structure of TSP to endogenous mucin may allow a formulation containing this polymer to adhere readily to the ocular surface for prolonged periods and provide sustained relief from the symptoms of dry eye [10]. Indeed, studies undertaken to date suggest that TSP may have some benefits over HA relating to ocular retention time, wound healing properties and relief of dry eye symptoms [8,11].

Overall, TSP has several physicochemical properties that make it suitable for the management of dry eye syndrome (Table 2) and which potentially have distinct advantages over currently available preparations.

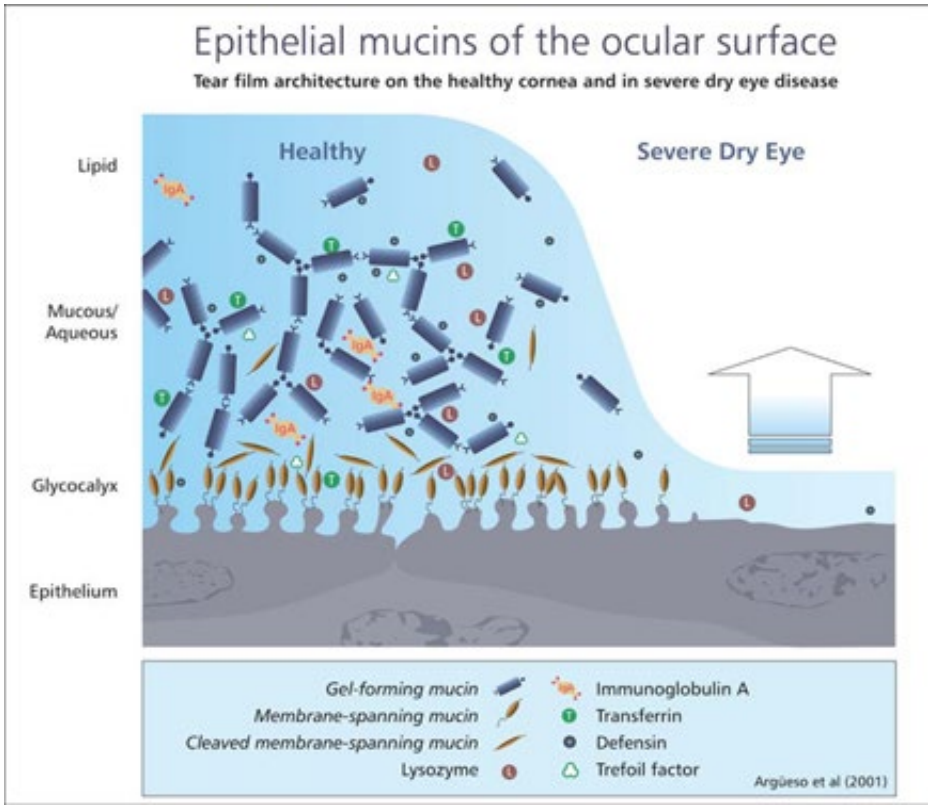

Figure 1
The location and extent of epithelial mucins on the ocular surface.

A study was performed to test this promising new agent against HA in the treatment of dry eye syndrome.

Methods

This open-label, randomised, comparative clinical study compared the activity of TSP 0.5% and 1% vs. HA 0.2% (Hyalistil™). A total of thirty patients with dry eye syndrome were recruited (TSP 0.5% n = 11; TSP 1% n = 10; HA 0.2% n = 9).

Patient demographics

Baseline characteristics of enrolled patients are summarised in Table 3.

Subjects were given three or more applications per day of the randomised study treatment over a period of 90 days. Patients were included if they were over 18 years of age, had a tear break-up time (BUT) < 10 seconds, dry eye symptoms (2 >6 cm on VAS), a Schirmer I test = 5 mm/5

Table 1: Characteristics of mucin-deficient dry eye

- Instability of tear film
- Presence of non-wetted areas on the corneal and conjunctival surfaces
- Decreased mucin production
- Altered mucin distribution
- Keratisation of the cornea and conjunctiva
- Loss of conjunctival goblet cells

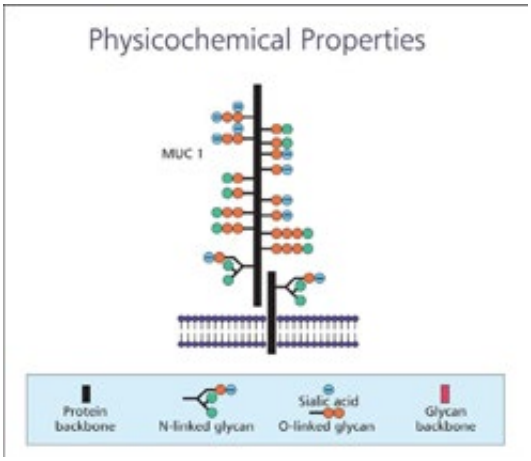

Figure 2
Configuration of TSP.

min and positive testing = 2 in at least one area of ocular surface. Patients were excluded if they were pregnant or breastfeeding, had eye surgery in the previous three months, were on other ocular therapies or had other eye pathologies.

The primary objective of this study was to evaluate the tolerability of topical ocular administration of TSP in patients presenting with dry eye. This was assessed by a specific VAS tolerability questionnaire and by data relating to adverse events. Secondary objectives were to evaluate improvement in the stability of the precorneal tear film with the study treatments and to assess any changes in subjective symptoms and ocular surface staining.

Table 4 shows the assessment of tolerability and performance.

Tolerability data were recorded throughout the study by means of a VAS questionnaire listed per single visit. The sum total of VAS scores for all the questions, recorded after 90 days of treatment for the three groups, was evaluated by ANOVA, followed by multiple comparisons by Tukey's test. Differences relating to the trend of this variable over the 90-day study period were evaluated by means of ANOVA for repeated measurements. Any adverse events received in the study were to be described in full detail and differences amongst treatment groups evaluated accordingly (chi-square test). All treated patients were recorded in the tolerability evaluation.

Subjects in the study were assessed on days 0 (baseline), 14, 30, 60 and 90. Data have been collected from both eyes of each patients in all groups. All data have been used for statistical analysis.

At baseline, the IOP ranged from 12–19 mmHg with no difference between treatment groups and the BUT mean values were around 5 seconds for all treatments, ranging from 3–8 seconds.

This trial was carried out in accordance with the Helsinki declaration and patients' informed consent was obtained prior to commencing the study. The Study was approved by the ethics committee of S. Martino Hospital in Genoa, Italy [12].

Results

In terms of the primary objective of evaluating tolerability, a questionnaire was used to detect the onset of blurred vision, ocular redness, ocular burning and ocular itching immediately after instillation of the preparations. For the entire duration of the study, there was no reported onset of any of the tolerability parameters assessed (Table 4). Furthermore, there were no adverse events reported throughout the study in any of the treatment groups.

Tables 5, 6, 7, 8, 9 present the results of the secondary objectives. Subjective symptoms were improved in all treatment groups (Table 5). However, there were some significant differences observed between the groups. TSP 1% showed benefits over HA in certain of the subjective VAS scores, with significant differences between treatments for the factors shown in Table 6. There were no inter-treatment differences (i.e. no superiority vs. comparator) for clinical measurements.

Furthermore, it was observed that TSP 0.5% and 1% demonstrated efficacy with significant inter-visit differences ($p < 0.05$) for the following:

• Subjective symptom improvements: Blinking trouble, ocular burning, sensation of foreign body, wish to keep eyes shut, photophobia, ocular pain

Table 2: Physicochemical properties of TSP

• Chemical structure similar to membrane-bound ocular mucins
• Non-Newtonian rheologic behaviour
• Ferning pattern similar to natural tear film
• Mucomimetic, mucoadhesive and pseudoplastic properties

Table 3: Demographic characteristics and medical history data*

	TSP 0.5% (n = 11)	TSP 1% (n = 10)	HA 0.2% (n = 9)
Gender			
Female	6 (54.5%)	6 (60.0%)	8 (88.8%)
Male	5 (45.4%)	4 (40.0%)	1 (11.1%)
Age (years)			
Mean (SD)	59.01 (13.83)	62.33 (13.06)	59.45 (10.60)
Min – Max	41.28 – 82.36	47.16 – 90.62	45.11 – 70.34
Sjogren's Syndrome	3 (27.3%)	4 (40.0%)	3 (33.3%)

* No statistically significant differences were observed between groups

• Performance improvements: Tear film break up time, corneal and conjunctival damage

Intraocular pressure

Concerning IOP, all treatments showed relatively stable values during the study period; mean values remained around 14–15 mmHg, ranging from 12–19 mmHg. Changes between baseline and day-60 visit (no assessment at final visit was foreseen) were negligible for all treatments and in both eyes.

Average number of daily instillations

The average number of daily instillations was found to be similar in three treatment groups throughout the study, ranging between 3 and 4 instillations with no statistically significant difference.

Tear film break up time (BUT)

In terms of tear film break up time, mean values are shown in Tables 7 and 8. Analysis of the time-course of values showed a significant increase in values between baseline and final visit (ANOVA between visits $p < 0.05$). There were no observed differences between treatments.

Corneal and conjunctival staining

Importantly, for both corneal and conjunctival damage in both eyes, there was a statistically significant decrease in total staining score between baseline and final visit in all three treatment groups, with no statistically significant differences observed between groups (Figure 3).

Discussion

TSP is a neutral polymer that, unlike the majority of viscosity enhancing polymers, has a branched-chain structure similar to that of corneal and conjunctival mucus transmembrane proteins. It has mucomimetic, mucoadhesive and pseudoplastic properties that may account for the benefits observed in improving dry eye signs and symptoms.

In this study comparing TSP with HA, all preparations demonstrated optimal tolerability, with no reported onset of blurred vision, ocular redness, ocular burning or ocular itching. This confirms their suitability, even for frequent use, as tear substitutes in the treatment of dry eye. Clinical performance was also demonstrated with all treatments.

Table 4: Assessment of tolerability and performance

Tolerability – primary objectives

a. VAS tolerability questionnaire to evaluate:
- Blurred vision
- Ocular redness
- Ocular burning
- Ocular itching

b. Adverse events

Performance – secondary objectives

- Clinical/symptomatologic evaluation (symptoms were evaluated using a VAS questionnaire recording: discomfort when blinking, burning, foreign body sensation, sensation of ocular fatigue/heaviness, sensation of tearing, desire to keep eyes closed, sensation of photophobia, sensation of blurred vision and sensation of pain)
- Corneal and conjunctival staining
- Intraocular pressure (IOP)
- Tear film break-up time (BUT)
- Number of daily instillations

Table 5: Results

	Blinking trouble*	Ocular burning**	Sensation of foreign body***	Sensation of lachrymation°	Ocular fatigue/ load sensation°	Wish to keep eyes shut°	Photophobia°
0.5% TSP (n = 11)							
Baseline Mean (SD)	81.55 (27.62)	86.09 (14.49)	89.64 (9.06)	8.64 (28.64)	25.45 (43.69)	31.45 (45.23)	8.82 (29.25)
Visit 5 (day 90) Mean (SD)	38.00 (22.46)	43.45 (13.92)	36.82 (15.42)	4.55 (15.08)	15.73 (27.38)	16.27 (24.69)	4.73 (15.68)
1% TSP (n = 10)							
Baseline Mean (SD)	81.20 (31.93)	93.00 (8.62)	90.50 (9.64)	9.50 (30.04)	9.70 (30.67)	40.60 (45.74)	14.70 (32.76)
Visit 5 (day 90) Mean (SD)	16.50 (16.21)	22.30 (13.70)	16.60 (16.79)	4.40 (13.91)	3.20 (10.12)	5.90 (10.35)	1.20 (3.79)
0.2% HA (n = 9)							
Baseline Mean (SD)	63.22 (40.39)	78.78 (30.76)	72.00 (31.08)	0.00 (0.00)	10.78 (32.33)	59.67 (45.17)	25.00 (38.98)
Visit 5 (day 90) Mean (SD)	40.67 (28.27)	50.44 (22.11)	42.78 (29.47)	0.00 (0.00)	9.33 (21.29)	28.67 (35.12)	12.44 (24.00)

* TSP 1% vs. HA 0.2%; $p < 0.05$
** TSP 1% vs. HA 0.2%; $p < 0.05$, TSP 1% vs. TSP 0.5%; $p < 0.05$
*** TSP 1% vs. HA 0.2%; $p < 0.05$
° p = NS

All study preparations produced an improvement in many of the subjective symptoms assessed. The significant differences between products in some subjective symptom scores are interesting and warrant further investigation in a larger study population. Of particular note is the significant improvement in scores observed with TSP 1% between baseline and final visits for symptoms relating to trouble blinking, ocular burning and sensation of foreign body. These results suggest that TSP 1% may improve patient quality of life (Table 6).

The results with BUT are particularly interesting. Under normal conditions, blinking generally occurs at an average of 10–15 movements per minute (one blink every 4–6 seconds). Reports of spontaneous eye blink rate vary widely however and in some situations may be less than seven blinks per minute (one blink every 8.5 seconds). It is desirable for the tear film to remain intact between blinks so that the eye surface is 'protected' and a BUT of 8 seconds is often taken as a target. This may not only produce a benefit in terms of symptoms but also interrupts the onset of the cycle of tear instability/epithelial injury/tear instability that maintains and worsens dry eye syndrome [13]. Indeed, reports even cite that a BUT >10 seconds is required to protect ocular surface [14].

Vital dyes such as fluorescein and rose bengal are commonly used in ophthalmology to assess the extent and severity of damage to the ocular surface epithelium [15]. Importantly, statistically significant improvements between baseline and final visits were observed with respect to corneal and conjunctival staining, suggesting an improvement in the health of the ocular surface epithelium.

Lastly, the inclusion criteria used have allowed for recruitment of patients with Sjögren's syndrome. An analysis of the sub-set of patients with this condition was performed for this trial and, although patient numbers were insufficient to reach significance, trends in these data suggest an improvement in BUT and symptom scoring with TSP in this challenging patient population.

TSP clinical studies to date have produced interesting results. A randomised, blinded four-way crossover scintigraphic investigation of precorneal residence time of 3 TSP concentrations (0.5%, 1.0% and 2.0%) and HA 0.4% was conducted in 12 patients with mild to moderate dry eye syndrome, aged between 35–75 years [11]. Whilst TSP 0.5% was found to have a comparable profile to HA 0.4%, dynamic corneal residence-time curves showed that TSP 1% and 2% formulations demonstrated greater retention than HA 0.4%. The authors concluded that this pattern of retention strongly suggests a tear-structuring effect of TSP [11].

There are some limitations and additional aspects to this study worth considering. The fact that varying TSP con-

Table 6: Dry eye symptoms: significant inter-treatment differences

Trouble blinking	TSP 1% vs. HA 0.2%; $p < 0.05$
Ocular burning	TSP 1% vs. HA 0.2%; $p < 0.05$ TSP 1% vs. TSP 0.5%; $p < 0.05$
Sensation of foreign body	TSP 1% vs. HA 0.2%; $p < 0.05$

Table 7: Tear film break up time (BUT)

	TSP 0.5% (n = 11)	TSP 1% (n = 10)	HA 0.2%(n = 9)
Baseline Mean (SD)	5.18 (1.33)	5.00 (1.33)	5.22 (1.79)
Day 15 Mean (SD)	6.64 (2.11)	6.20 (1.48)	6.00 (2.18)
Day 30 Mean (SD)	7.64 (1.96)	7.20 (1.55)	6.78 (2.28)
Day 60 Mean (SD)	8.45 (2.30)	8.30 (1.42)	8.00 (2.65)
Day 90 Mean (SD)	9.64 (2.29)	9.40 (1.35)	8.44 (2.51)

Table 8: BUT – changes from baseline to final visit (90 days)

Treatment	n	Mean
0.5% TSP	11	4.45*
1% TSP	10	4.40*
0.2% HA	9	3.22*

* ANOVA between treatments; $p < 0.05$

Table 9: Summary of trial results of TSP vs. HA 0.2%

- TSP is effective at concentrations of 0.5% and 1% in treating dry eye syndrome, demonstrated by its effect on tear film break up time, corneal and conjunctival damage and its ability to provide symptom relief over a 90 day period
- TSP 0.5% and 1% show equivalent performance to HA 0.2% with regard to improving tear film break up time
- TSP 1% produced a significantly greater effect compared with HA 0.2% in some patient-scored symptoms

centrations and HA are distinguishable by appearance, viscosity and delivery device necessitates the use of an open label trial. In addition, as the trial was not placebo-controlled, patients were aware of receiving an intervention and, therefore, it is possible that this may have impacted on patients' subjective scoring of dry eye symptomatology.

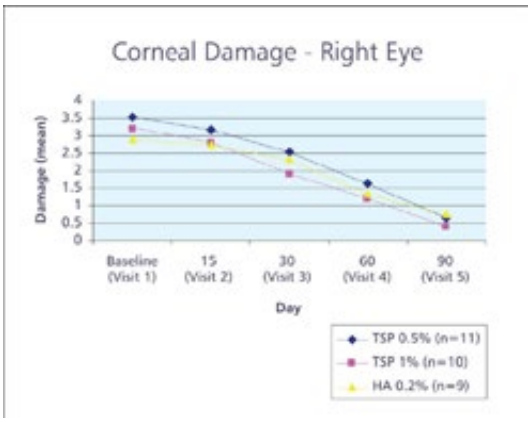

Figure 3
Graph showing corneal staining total score over time.

Conclusion

This study has demonstrated that TSP 0.5% and 1% are comparable to HA 0.2% according to the variables measured in the study. Due to the absence of both onset and incidence of adverse events reported throughout the study, it is concluded that all treatments demonstrated optimal tolerability and are suitable for frequent use in the therapy of dry eye. Statistically significant improvements between baseline and final visits were observed with respect to tear film break up time and corneal and conjunctival damage.

However, the results obtained with the subjective VAS symptom scores suggest benefits of the TSP 1% formulation (Table 9). It is possible that the effects seen with TSP could translate into significant differences in objective clinical measurements in a larger study population. Furthermore, data analyses indicate that TSP might, over a period of time, produce improvement in tear film stability, thereby improving eye conditions and overall patient quality of life.

Abbreviations

HA Hyaluronic acid

TSP Tamarind seed polysaccharide

VAS Visual Analogue Scale

BUT Break up time

MUC1 conjunctival mucin 1

IOP Intraocular pressure

Competing interests
The author(s) declare that they have no competing interests.

Authors' contributions
RM: conceived of the study, and participated in its design and coordination, performed the study and the initial writing of the the draft manuscript.

CV: participated in the design of the study and performed the statistical analysis.

Both authors read and approved the final manuscript.

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Eficacia del tratamiento de dos meses con Xiloial ® colirio para las molestias de las lentes de contacto blandas desechables

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Resumen

Objetivo:

Evaluar la eficacia y la tolerabilidad del colirio monodosis Xiloial ® en el tratamiento de pacientes que padecen síntomas subjetivos de malestar relacionados con el uso de lentes de contacto blandas desechables (dSCL).

Métodos:

Se inscribieron quince usuarios de dSCL (12 mujeres, tres hombres, edad media 39 ± 9 años). Los criterios de inclusión fueron puntuación del cuestionario de síntomas del Índice de enfermedad de la superficie ocular (ODSI) >12, tiempo de ruptura de la película lagrimal (TFBUT) <10 s, prueba de Schirmer I >10 mm durante cinco minutos, queratopatía puntuada leve y tinción conjuntival (graduación de Oxford ≤ 4). Se administraron colirios monodosis de Xiloial tres veces al día durante un período de dos meses. Los pacientes fueron evaluados en el momento de la inscripción, después de tres días de lavado (línea de base) y después de uno y dos meses de tratamiento, mediante puntuación OSDI, prueba de Schirmer I, TFBUT, prueba de Ferning, daño de la superficie ocular (grado de Oxford) y albúmina sérica en lágrimas. (índice de exudación pasiva relacionada con la fuga de suero).

Resultados:

Al final versus al inicio, respectivamente, la media ± desviación estándar de todas las variables mejoró de la siguiente manera: OSDI (8,5 ± 3 versus 20,2 ± 1,6); TFBUT (9,6 ± 1,1 frente a 7,1 ± 1,0); calificación de Oxford (0,5 ± 0,1 versus 3,6 ± 0,8); prueba de helecho (2 ± 1 versus 2,4 ± 0,5); y prueba de Schirmer I (14,6 ± 1,1 versus 12 ± 2,1), con $P < 0,05$ para todas las variables (pruebas de Friedman y Wilcoxon). La tolerabilidad fue alta y no se observaron eventos adversos.

Conclusiones:

Un tratamiento de dos meses con Xiloial mostró buena tolerancia y pareció reducir el daño de la superficie ocular y los síntomas de incomodidad.

Palabras clave: malestar, ojo seco, lentes de contacto desechables, biopolímero polisacárido de semilla de tamarindo–ácido hialurónico

Ir a:

Introducción

Los síntomas de malestar en la superficie ocular son comunes en los usuarios de lentes de contacto y afectan a aproximadamente la mitad de ellos. [1,2] Hasta el 20 % de los usuarios de lentes de contacto experimentan síntomas que son lo suficientemente graves como para reducir el tiempo de uso. [3,4] Además, entre el 12 % y el 24 % de los pacientes que usan lentes de contacto dejan de usar lentes de contacto de forma permanente. [4,5] La razón más común para dejar de usar lentes es la incomodidad, que afecta a alrededor del 49 % al 72 % de los usuarios. [5-7] Otros síntomas que afectan con frecuencia a los usuarios de lentes son sequedad, picazón, sensación de arenilla, fotofobia, molestias y dolor. [4]A pesar de esto, el 65% de los usuarios de lentes de contacto piensan que esta es la forma ideal de corrección visual. [4] El mecanismo especulado de la incomodidad y la

sequedad relacionadas con los lentes de contacto es multifactorial, incluida la evaporación, [8] la hipoestesia, [9] la disminución de la producción de lágrimas con un aumento simultáneo de la osmolaridad, [10] y la inflamación. [11-13]

La película lagrimal es fundamental para el uso exitoso de lentes de contacto. Una película lagrimal estable es importante para promover una visión clara y reducir la aberración óptica creada por la ruptura de la película lagrimal. [14] La instilación de sustitutos de lágrimas puede mejorar la calidad óptica de la visión en el síndrome del ojo seco relacionado con lentes de contacto, [15,16] y las formulaciones de sustitutos de lágrimas sin conservantes son preferibles debido a la toxicidad de los conservantes. [17]

Los conceptos en evolución en la formulación de sustitutos de lágrimas sugieren que se puede lograr un mejor cumplimiento mejorando la estabilidad de la interfaz entre la película lagrimal y el epitelio corneal con propiedades mucoadhesivas y un mayor tiempo de retención en la superficie. [17] Además, un sustituto hipotónico puede reducir la hiperosmolaridad lagrimal, una característica común en cualquier tipo de enfermedad relacionada con el ojo seco. [18]

El presente estudio evaluó la eficacia y la tolerabilidad de un tratamiento de dos meses en usuarios sintomáticos de lentes de contacto blandas desechables con un innovador copolímero hipoosmolar sin conservantes ya disponible comercialmente en Italia (Xiloial ® colirio; Farmigea, Pisa, Italia), formulado para fortalecer las propiedades sinérgicas del ácido hialurónico y el polisacárido de semilla de tamarindo (TSP).

Ir a:

Métodos

Población de estudio

Quince usuarios de lentes de contacto desechables (12 mujeres de 40 ± 9 años, tres hombres de 37 ± 9 años) se inscribieron en un sitio de investigación en Bolonia, Italia. Los pacientes eran usuarios de lentes de contacto a tiempo completo, y la marca y el material del tipo de lente de contacto, el programa de reemplazo y las soluciones utilizadas se informan entabla 1. El estudio fue aprobado por el Comité Ético Independiente y realizado de acuerdo con los principios éticos de la Declaración de Helsinki y la legislación vigente sobre investigación clínica en Italia. Todos los sujetos firmaron un formulario de consentimiento informado antes de comenzar el estudio.

tabla 1

Los tipos de lentes de contacto (marca y material), programa de reemplazo, soluciones, tiempo de uso (años y diario) se enumeran para cada paciente inscrito

Paciente	Desgaste/día (horas)	Desgaste/total (años)	Material	Horario de reemplazo	solución para lentes de contacto	intolerancia pasada
1	10	5	Iotrafilcon A	1 día	ninguna	sí
2	10	8	EtafilcónA	15 días	Libre de Opti	no
3	10	5	EtafilcónA	1 día	ninguna	sí
4	10	5	OmafilcónA	1 día	ninguna	sí
5	10	5	EtafilcónA	1 día	ninguna	sí
6	8	1	HilafilcónB	1 día	ninguna	no
7	10	5	NelfilcónA	1 día	ninguna	sí
8	10	8	polimacón	15 días	ReNu Multi Plus	no
9	10	8	GalifilcónA	7 días	AOSeptiembre	no

Paciente	Desgaste/día (horas)	Desgaste/total (años)	Material	Horario de reemplazo	solución para lentes de contacto	intolerancia pasada
10	12	10	Iotrafilcon A	1 día	ninguna	sí
11	12	12	Hilafilcón B	1 día	ninguna	sí
12	12	10	Etafilcón A	15 días	Libre de Opti	no
13	8	5	polimacón	15 días	ReNu Multi Plus	no
14	8	12	Etafilcón A	15 días	AOSeptiembre	no
15	12	12	polimacón	15 días	ReNu Multi Plus	no
Media ± DE	10,1 ± 1,4	7,6 ± 2,8				

Abrir en una ventana separada

Abreviatura: SD, desviación estándar.

Materiales

Se usó solución salina estéril (0,9% NaCl; Mini-Plasco, B. Braun, Meisungen, Alemania) para el período de lavado. Como solución de prueba se utilizó colirio Xiloial monodosis (ácido hialurónico al 0,2 % y TSP al 0,2 %, 280 mosm/l, pH 7,4).

Diseño del estudio

Este fue un estudio prospectivo, abierto y de un solo centro para investigar el efecto del tratamiento con Xiloial sobre la incomodidad en usuarios de lentes de contacto desechables sin suspender el uso de lentes durante el período de tratamiento. El estudio incluyó cuatro visitas durante dos meses, es decir, visita 0 (V0, cribado), visita 1 (V1, día 0/basal, realizada 1-3 días después de V0), visita 2 (V2, realizada 30 días después de V1), visita 3 (V3, punto final, 60 días después de V1).

Los criterios de inclusión y exclusión

Se incluyeron pacientes mayores de 18 años, con puntaje >12 en el cuestionario de síntomas del Ocular Surface Disease Index (OSDI), tiempo de ruptura de la película lagrimal (TFBUT) 19 menor a 10 segundos y prueba de Schirmer I >10 mm en cinco minutos . Se excluyeron pacientes con queratopatía puntuada >1 según grado Oxford [20] , así como mujeres embarazadas, personas con patologías de la superficie ocular concurrentes, cirugía ocular en los últimos seis meses, tratamiento ocular concomitante (excepto sustitutos de lágrimas) o con alérgico a alguno de los componentes de Xiloial (Tabla 2).

Tabla 2

Métodos y pruebas utilizados en el estudio, enumerados en secuencia de ejecución

Secuencia de prueba	Base	Valores a registrar	Valores patológicos
1. Cuestionario OSDI	Síntomas subjetivos	puntuación 1-100	>12 [19]
2. Prueba de Schirmer I	Medida indirecta de la secreción total de lágrimas	humectación mm en cinco minutos	≤5 mm/5 min [21]
3. Prueba de helecho	Un índice de estabilidad lagrimal	Grado I/IV	≥Grado II/III [22]
4. Recolección de lágrimas para la dosificación de albúmina.	Un índice de ruptura de la barrera sanguínea y exudación pasiva.	mg/mL	≥0,130 mg/mL [31]
5. TFBUT	Un índice de estabilidad de la película lagrimal	Segundos	≤10 seg [21]
6. Calificación de Oxford	Un índice de daño en la superficie ocular	Grado 0-3 para seis áreas	≥9/18 [20]

Abrir en una ventana separada

Abreviaturas: OSDI, Índice de enfermedad de la superficie ocular; TFBUT, tiempo de ruptura de la película lagrimal.

Procedimiento

En la visita de selección, se registró la información demográfica de los sujetos, junto con el uso actual/anterior de medicamentos, sustitutos de lágrimas y patologías oculares. Los sujetos que cumplieron con los criterios de inclusión firmaron el consentimiento informado y se inscribieron. Luego se les administró solución salina como lavado para minimizar cualquier efecto del uso previo de medicamentos. Se indicó a los sujetos que usaran las gotas de solución salina tres veces al día en ambos ojos y que se abstuvieran de administrar otras gotas de lágrimas después de las 8:00 am del día de su próxima visita.

Después de 1 a 3 días, los sujetos regresaron (V1) para el examen de seguimiento de elegibilidad, en el que se repitieron el TFBUT, la prueba de Schirmer I y el cuestionario OSDI. Además, se realizó la prueba de helecho y medición de albúmina sérica exudada en lágrimas. A los sujetos que seguían siendo elegibles para el estudio se les administraron gotas para los ojos monodosis de Xiloial y se les indicó que usaran una gota en cada ojo (al despertarse sin lentes de contacto, temprano en la tarde con lentes de contacto y antes de acostarse sin lentes de contacto).

Después de 30 (± 2) días (V2), los sujetos regresaron para el seguimiento. Se repitieron las mismas mediciones y preguntas del examen que para el V0, excepto la prueba de helecho y la medición de la albúmina sérica. La tolerabilidad se evaluó mediante la puntuación de una escala analógica visual de síntomas específicos (borrosidad, enrojecimiento, picazón, escozor después de la instilación) y se registraron los eventos adversos.

Luego se repitió el mismo examen que para V0 después de otros 30 (± 2) días (V3), lo que representó el punto final del estudio.

Las visitas al consultorio se realizaron después de la extracción de los lentes de contacto, y las condiciones fueron las mismas para todas las visitas en el sentido de que se realizaron aproximadamente a la misma hora del día (a primera hora de la tarde) y en una

habitación con poca luz y temperatura y humedad controladas. Dos examinadores independientes (VP y NB) realizaron un examen biomicroscópico con lámpara de hendidura en todas las visitas para registrar cualquier anomalía en la conjuntiva, párpados/pestañas, cámara anterior, iris y cristalino.

TFBUT se midió y registró (promedio de tres mediciones) utilizando 5 µL de fluoresceína sódica (Fluoralfa 0,25%; Alfa Intes, Casoria, Italia). La prueba de Schirmer I se realizó utilizando tiras reactivas estériles validadas (ContaCare Ophthalmics and Diagnostics, Gujarat, India), como se describe en otra parte. [21] Para cuantificar el daño de la superficie de la córnea y la conjuntiva, la tinción con fluoresceína sódica se comparó con gráficos estándar de acuerdo con el sistema de clasificación de Oxford, [20] con la ayuda de un filtro de barrera amarillo Kodak Wratten 12. La prueba de helecho se realizó como se describió anteriormente [22]al inicio y al final. Los patrones de arborización (helecho) de una gota de lágrima recolectada del menisco inferior y que se dejó secar por evaporación se clasificaron como Tipos I–IV (Tipo I, arborización uniforme; Tipo II, comienzan a aparecer espacios vacíos entre los helechos; Tipo III , los helechos individuales son pequeños, incompletos con ramificación rara o nula; Tipo IV, sin helechos), donde los Tipos I y II se reportan como normales, y los Tipos III y IV se reportan como anormales. [22]

La albúmina sérica exudada se midió al inicio y al final en muestras de lágrimas utilizando un kit comercial de ensayo inmunoabsorbente ligado a enzimas (Bio-Rad, Hercules, CA) de acuerdo con las instrucciones del fabricante, y se recogieron 10 µL de lágrimas no estimuladas de cada sujeto utilizando una micropipeta de laboratorio. (Pipetman ® ; Gilson Intl BV, La Haya, Países Bajos) con una punta desechable estéril.

análisis estadístico

Recolectamos datos para el ojo más incómodo, o arbitrariamente para el ojo derecho en caso de equivalencia. Los datos se analizaron

estadísticamente utilizando el software SPSS 9.0 (SPSS Inc., Chicago, IL) y MedCalc 5.0 (MedCalc Software, Mariakerke, Bélgica). Se aplicó la prueba de pares emparejados de Wilcoxon para los datos de helechos y albúmina, mientras que la prueba no paramétrica de Friedman para pares se usó para evaluar todas las demás variables. Los valores de $P \leq 0,05$ se consideraron estadísticamente significativos. Se realizaron estadísticas descriptivas para todas las variables, es decir, media y desviación estándar (DE). Se aplicó el análisis de correlación de Spearman para verificar la relación entre las variables y los datos del régimen de lentes de contacto usados, su duración y cualquier antecedente de intolerancia.

Ir a:

Resultados

Todos los sujetos completaron con éxito el estudio. Los datos se resumen enTabla 3y graficado enFigura 1a–f. No se observaron cambios significativos en ninguna de las pruebas aplicadas entre las visitas de selección y de referencia.

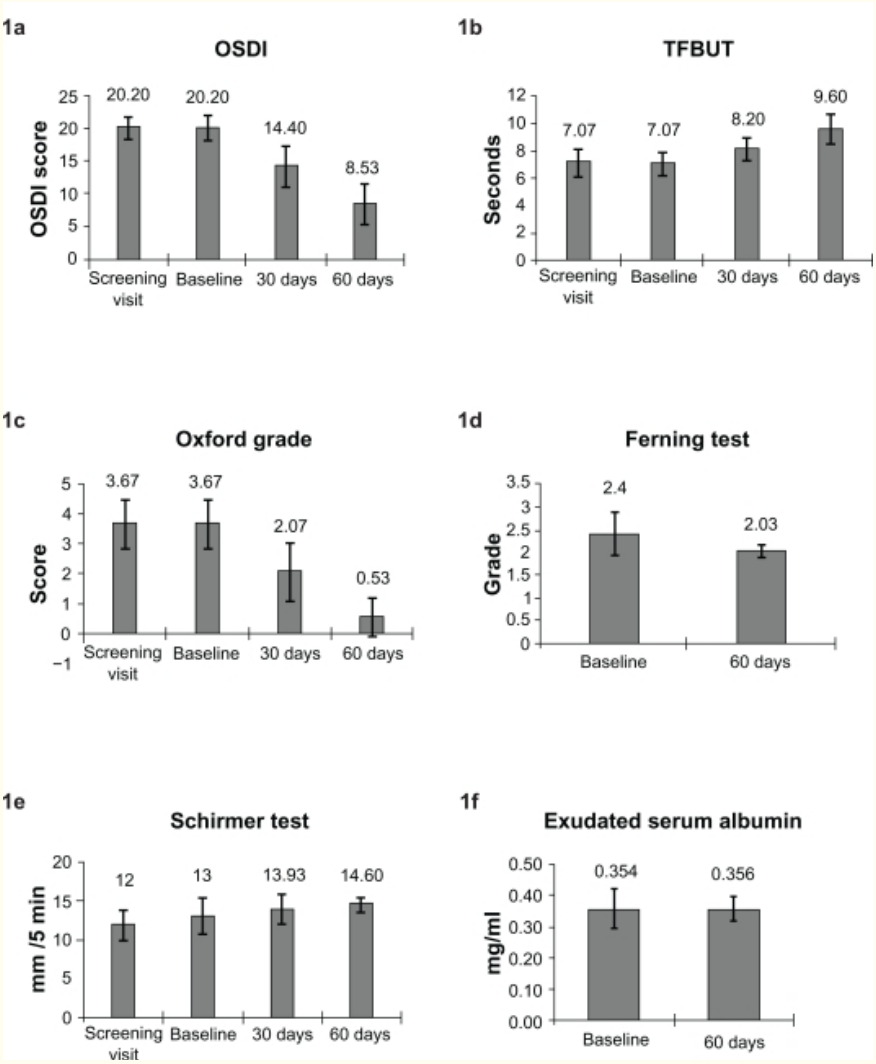

Figura 1

Los datos para cada variable y punto de vista analizado se representan gráficamente (media ± DE).

Tabla 3

Resumen de los resultados del estudio

Parámetro *	Visita de selección	Base	30 dias	60 días	Nivel de significación $P < 0,05$
OSDI	20,20 ± 1,66	20,20 ± 1,78	14,40 ± 2,97	8,5 ± 3,00	$P < 0,05$ (prueba de Friedman)

Parámetro *	Visita de selección	Base	30 dias	60 días	Nivel de significación $P < 0,05$
TFBUT	7,07 ± 1,03	7,07 ± 0,80	8,20 ± 0,77	9,60 ± 1,12	$P < 0,05$ (prueba de Friedman)
calificación de oxford	3,67 ± 0,82	3,67 ± 0,82	2,07 ± 0,96	0,53 ± 0,64	$P < 0,05$ (prueba de Friedman)
prueba de helecho	–	2,4 ± 0,47	–	2,03 ± 0,13	P <0,05 (prueba de Wilcoxon)
Prueba de Schirmer I	12 ± 2,10	13 ± 2,36	13,93 ± 1,91	14,60 ± 1,06	$P < 0,05$ (prueba de Friedman)
Albúmina sérica exudada	–	0,354 ± 0,06	–	0,356 ± 0,03	NS (prueba de Wilcoxon)

Abrir en una ventana separada

Nota:
* Media ± desviación estándar.
Abreviaturas: OSDI, Índice de enfermedad de la superficie ocular; TFBUT, tiempo de ruptura de la película lagrimal; NS, no significativo.

Síntomas de malestar ocular

Se encontró una disminución progresiva y significativa de los síntomas de malestar después de un mes de tratamiento. Al final, la puntuación OSDI se redujo a más de la mitad de la registrada al inicio del estudio (Tabla 3,Figura 1a). Todos los pacientes mostraron homogéneamente la misma tendencia y no se encontró correlación entre el tiempo de recuperación de los síntomas y ningún parámetro de uso de lentes de contacto.

Tiempo de ruptura de la película lagrimal

Se encontró un aumento significativo en TFBUT después de un mes de tratamiento, que aumentó aún más en la visita final, igualando los resultados con respecto al inicio (Tabla 3,Figura 1b). Se registró un aumento progresivo de los valores de TFBUT en todos los pacientes en ambos ojos.

Daño en la superficie ocular

El daño epitelial de la superficie ocular (según la puntuación de clasificación de Oxford) se redujo significativamente en seis de 15 pacientes después de un mes de tratamiento. La puntuación de daño desapareció al final del tratamiento de dos meses en ocho de 15 pacientes, a pesar del uso continuo de lentes de contacto (Tabla 3,Figura 1c). Se encontraron residuos de tinción conjuntival muy leves (puntuación 1 o 2) en los siete pacientes restantes al final del estudio. El tiempo de recuperación del daño no pareció estar relacionado con ningún parámetro de uso de lentes de contacto.

prueba de helecho

El grado de Ferning se redujo en ocho sujetos y no cambió en siete sujetos después de dos meses de tratamiento. El análisis estadístico demostró una reducción significativa ($P = 0,03$) de los valores al final frente al valor inicial (Tabla 3,Figura 1d).

valor de Schirmer

Cuatro pacientes no mostraron ningún cambio en el valor de Schirmer, mientras que en los 11 pacientes restantes se observó un aumento leve. El valor de Schirmer aumentó significativamente al final y fue evidente solo después de dos meses de tratamiento (Tabla 3,Figura 1e).

Albúmina en lágrimas

Se obtuvieron resultados no homogéneos para la albúmina sérica exudada en las lágrimas. Al analizar los datos en su conjunto, no se demostró una diferencia estadísticamente significativa en el punto final frente al valor inicial (Tabla 3,Figura 1f). Solo el subgrupo de pacientes que no había experimentado ninguna intolerancia al uso de lentes de contacto en el pasado mostró una disminución estadísticamente significativa en la albúmina sérica exudada al final frente al valor inicial (0,359 ± 0,04 frente a 0,388 ± 0,03, $P = 0,007$, prueba de Wilcoxon), pero no hubo correlación se encontró con otras características de uso de lentes de contacto.

tolerabilidad

El cuestionario de tolerabilidad de la escala analógica visual mostró una muy buena respuesta al tratamiento. No se informó visión borrosa, enrojecimiento ocular, ardor o picazón, ni ningún evento adverso.

Ir a:

Discusión

Xiloial es una nueva preparación oftálmica basada en la acción sinérgica única de TSP y ácido hialurónico de alto peso molecular obtenido por síntesis biotecnológica.

La TSP es un polímero neutro que muestra una estructura de cadena ramificada similar a la de las proteínas transmembrana del moco conjuntival y corneal, específicamente MUC1. Esta estructura particular explica las propiedades distintivas mucomiméticas, mucoadhesivas y pseudoplásticas [23,24] que hacen que la TSP sea adecuada para el tratamiento de los signos y síntomas del ojo seco. El ácido hialurónico (también llamado hialuronato de sodio) es un polímero no newtoniano que muestra un buen tiempo de retención en la superficie ocular, tiene una viscosidad ya en baja concentración, lo que reduce las tensiones de fricción durante el parpadeo y estabiliza la película lagrimal, lo que retrasa la evaporación de las lágrimas. [25]

La acción de estos dos agentes en formulaciones separadas se ha investigado en el pasado [26,27] en el ojo seco relacionado con el uso de lentes de contacto. Hasta donde sabemos, la presente investigación es la primera en analizar el efecto sinérgico de una nueva formulación que contiene ambos agentes utilizados en usuarios de lentes de contacto.

Los usuarios de lentes de contacto que tenían un régimen de reemplazo de menos de un mes fueron seleccionados para este estudio porque este horario se está volviendo popular en muchos países. [28] Como ya se informó, la interrupción del uso de lentes de contacto está estrictamente relacionada con la aparición de síntomas de incomodidad, que al principio reducen el uso diario y luego progresan hasta el abandono del uso de lentes de contacto si el manejo y la terapia no tienen éxito. [4]

Los pacientes incluidos en nuestro estudio habían usado lentes de contacto de forma continua durante cinco años o más, y aproximadamente la mitad de ellos habían experimentado intolerancia previa a los lentes de contacto. Todos los pacientes mostraron un buen cumplimiento del tratamiento con Xiloial, con una tolerabilidad óptima y sin efectos adversos. En este sentido, ninguno de los pacientes informó de visión borrosa, picazón o rascado después de la instilación de prueba mientras usaba sus lentes de contacto.

Se observó una reducción estadísticamente significativa de los síntomas subjetivos después de un mes de tratamiento, y en 12 de 15 pacientes el valor OSDI alcanzó la puntuación normal de los síntomas al final del estudio. En nuestra opinión, los síntomas subjetivos residuales podrían estar relacionados con el uso continuo de lentes de contacto en sí, aunque no se encontró relación con el régimen de lentes de contacto.

Se demostró un aumento estadísticamente significativo en los valores de TFBUT en todos los pacientes paso a paso con la duración del tratamiento, pero ningún sujeto alcanzó el valor normal de TFBUT de más de 10 segundos. Por otro lado, el uso continuado de lentes de contacto durante el tratamiento podría explicar estos resultados, ya que se reconoce que una disminución de TFBUT es un efecto secundario importante de los lentes de contacto. [29]

Siete de 15 pacientes mostraron un grado de helecho lagrimal normal al inicio del estudio, incluso en presencia de síntomas subjetivos de incomodidad, lo que parece estar en desacuerdo con autores anteriores que han demostrado que el helecho lagrimal es un buen predictor de tolerancia exitosa al uso de lentes de contacto. [30] Como se sugirió anteriormente, [21] la interpretación del helecho lagrimal parece estar relacionada con el contenido iónico de las lágrimas. En este estudio, el helecho lagrimal pareció significativamente reducido en comparación con los valores normales después del tratamiento, posiblemente debido a la dilución lagrimal realizada por el sustituto.

El daño epitelial de la superficie tanto de la córnea como de la conjuntiva se redujo significativamente después de un mes de tratamiento, y se mostró una curación epitelial completa en 19 de 30 ojos en el punto final. Este resultado es particularmente interesante si se considera que la integridad epitelial se restauró después del tratamiento, incluso en presencia del uso de lentes de contacto en el lugar. Esta observación respalda la acción mucomimética de Xiloial y su capacidad para desempeñar un papel protector como polímero que se interpone entre el epitelio corneal y la lente de contacto.

Los pacientes habían sido seleccionados ad hoc con valores de Schirmer I normales como criterio de inclusión para este estudio con el fin de reducir las variables del estudio y reclutar pacientes con molestias subjetivas leves. Se observó un aumento pequeño, pero estadísticamente significativo, en el valor de Schirmer al final del estudio en comparación con el valor inicial. Sin embargo, la confiabilidad de la prueba de Schirmer ha sido debatida recientemente debido a los grandes coeficientes de variación en medidas repetidas, a menos que se trate de valores inferiores a tres mm de longitud de banda húmeda. [31] Por lo tanto, es factible que el aumento de 2 mm en los valores de Schirmer observado en nuestro estudio esté más relacionado con la variabilidad de la prueba que con la eficacia del tratamiento.

La albúmina sérica en las lágrimas se considera un índice indirecto de inflamación como consecuencia de la exudación pasiva debido al aumento de la fuga de los vasos sanguíneos. [32] Ya se han informado en la literatura niveles elevados de albúmina sérica en las lágrimas de los usuarios de lentes de contacto y, cuanto mayor sea la concentración, mayor será el grado de depósito que se puede esperar en el lente, particularmente para el ojo seco. [33]El análisis estadístico apareado de todos los pacientes no mostró ninguna diferencia estadísticamente significativa en el contenido de albúmina sérica en las lágrimas. Curiosamente, solo se mostró una disminución significativa en la albúmina sérica exudada en el subgrupo de pacientes que no habían informado previamente episodios únicos o repetidos de intolerancia al uso de lentes de contacto. Se mostró un aumento leve, pero no significativo, en el subgrupo de pacientes que reportaron intolerancia previa a las lentes de contacto. Reconocemos que no se pueden sacar conclusiones del presente estudio debido al número limitado de pacientes, pero se puede especular que la respuesta conjuntival puede cambiar después de la intolerancia, como se ha sugerido para las lentes de contacto nocturnas. [34]

Como observación final, un tratamiento de dos meses con el copolímero Xiloial ® de nueva formulación en usuarios de dSCL sintomáticos que aún usaban el dispositivo mostró:

- alta tolerabilidad
- reducción de los síntomas subjetivos
- reducción del daño epitelial de la superficie ocular
- aumento en el valor TFBUT
- reducción de la albúmina sérica exudada en las lágrimas en aproximadamente la mitad de los pacientes.

Ir a:

notas al pie

Divulgación

Los investigadores no tienen ningún interés de propiedad en el producto probado. No se han hecho arreglos financieros en los que el resultado del estudio pueda afectar la compensación.

Ir a:

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RESUMEN DEL PRODUCTO

Zonaker®T

Hialuronato de Sodio 0.2%, TS-Polisacárido 0.2%

Molécula	TSP* 0.2%+ HA** 0.2%
Registro	Dispositivo médico.
Fórmula farmacéutica	Solución oftálmica lubricante e hidratante 10 mL
Indicación	Proporciona una lubricación y alivio duraderos al ojo seco causado por elementos ambientales (viento, sol, agua salada, humo, aire acondicionado, calefacción), uso excesivo de computadora o factores mecánicos (cirugía ocular, uso de lentes de contacto) protegiendo la córnea y conjuntiva
Dispositivo	Dispositivo Novelia 25 gotas por mL
Posología	Se recomienda administrar una gota de solución oftálmica, en el fórnix conjuntival, una o más veces al día según necesidad.

*TSP: Polisacárido de la semilla de tamarindo, por sus siglas en inglés **HS: Hialuronato de sodio

Sus pacientes encuentran Zonaker®T en todas las principales cadenas de farmacias.

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