Softdrops

EYE DROPS

Carboxymethyl cellulose 0.5% + Glycerin 0.5% + N-Acetyl Carnosine

Comprehensive Management in Dry Eyes...

Product Monograph

Most of the Tear drops Comes with Only Lubrication!

Introducing

Softdrops

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Comprehensive Management in Dry Eyes...

Goes Beyond Lubrication!

TABLE OF CONTENTS

Section I

DRY EYES

Introduction

The cornea, conjunctiva, and accessory lacrimal glands that make up the ocular surface, the lipid producing sebaceous glands of the eyelid margin or the meibomian glands, and the main lacrimal gland are the 3 functional units to be affected in dry eye disease (DED). Dry eye syndrome (keratoconjunctivitis sicca) is a multifactorial disease that results in eye discomfort and visual disturbance that substantially affects the quality of life due to inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency and meibomian gland dysfunction.[1] Dry eye disease has an inconsistent global prevalence rate of up to 34%.

Major forms of dry eye disease

A Tear Film and Ocular Surface Society Dry Eye Workshop II subcommittee recently updated a dry eye classification scheme based on cause, vision effects, mechanism, and disease severity. It is important for clinicians to consider the evaporative dry eye and aqueous-deficient dry eye forms as they diagnose, treat, and monitor dry eye, since risk factors, causes, and treatment vary according to the form and subtype (Fig. 1).[2] Aqueous-deficient dry eye is characterized by decreased secretion of tears from the lacrimal glands, whereas evaporative dry eye results from increased evaporation of tear fluid from the eye surface. These conditions are not mutually exclusive; in fact, they often overlap. Environmental factors also play a role in dry eye by perturbing mechanisms of tear film homeostasis.

Fig. 1 Two major forms of DED

Evaporative dry eye

- Meibomian oil deficiency
- Disorders of lid aperture
- Low blink rate
- Drug action (e.g., isotretinoin)
- Vitamin A deficiency
- Topical drugs and preservatives
- Contact-lens use
- Other ocular surface disease (e.g., allergy)

Aqueous-deficient dry eye

Related to Sjögren's syndrome

- Primary Sjögren's syndrome
- Secondary Sjögren's syndrome (e.g., with rheumatoid arthritis)

Not related to Sjögren's syndrome

- Aging
- Lacrimal deficiency
- Systemic drugs
- Lacrimal-gland duct obstruction
- Graft-versus-host disease
- Congenital abnormalities of lid or gland
- Underlying connective-tissue disease
- Reflex block
- Neuropathic disorders
- Contact-lens use

Four dry eye subtypes

Due to tear-film instability

- Blepharitis (e.g., meibomian-gland disease)
- Contact-lens use
- Vitamin A deficiency

Due to somatosensory dysfunction

- Neuropathic disorders
- LASIK and refractive surgery
- Hypesthesia

Due to toxicity

- Antiglaucoma medications
- Systemic cytotoxic medications (e.g., methotrexate)
- Preservatives in topical solutions

Anatomically related dry eye

- Congenital abnormalities
- Thyroid eye disease
- Lacrimal-gland obstruction
- Lid abnormalities
- Chalasis

Dry eye – Epidemic of changing lifestyle

Titiyal JS et al. determined the prevalence of dry eye disease to be 32% (5000/15625); in which 9.9% (496/5000) had mild dry eye disease; 61.2% (3060/5000) had moderate dry eye disease; and 28.9% (1444/5000) had severe dry eye disease.[3] Significant correlation was seen with dry eye disease and hours of visual display terminal (VDT) usage ($P < 0.001$). Severe dry eye was seen in 89.98% of patients with 4 h or more of VDT use. Uchino et al. also reported high incidence of dry eye disease among computers, laptops, tablets and large screen mobile phones VDT users. Significantly greater odds of developing severe dry eye disease were also seen with cigarette smoking and contact lens usage ($P < 0.001$). The incidence of dry eye disease in the exposed population is also associated greater air pollution.

Eye strain and sedentary behavior are also important contributors to the development of DED. In a study, the tear film breakup time and ocular surface staining scores were significantly associated with International Physical Activity Questionnaire scores; and furthermore, tear film breakup time was significantly associated with sedentary time.[4,5] Office workers who were sitting for long hours in front of visual display terminals (VDTs) tend to exhibit sympathetic dominance and suffer from dry eye disease.[6] Lifestyle factors are also associated with DED (in addition to prolonged VDT exposure), and therefore lifestyle intervention, including exercise and an appropriate diet with conventional topical treatment are promising treatment strategies for DED. Thus, strategies for DED management are mainly becoming preventive in nature. There is clear evidence regarding the benefits of exercise for patients with various systemic diseases, including physical (e.g., DM) and mental (e.g., depression) diseases.[7]

Amalgamation of multiple risk factors

Fig. 2 Amalgamation of multiple risk factors

- Age. Dry eyes are a part of the natural aging process.
- Post menopause and possibly hormone replacement therapy.
- Medical conditions - Rheumatoid arthritis, diabetes, thyroid problems, blepharitis/ meibomian gland disease, rosacea, seborrhoeic dermatitis, staphylococcal infection, Demodex mite infestation, inflammation of the surfaces of the eye, or the inward or outward turning of eyelids.
- Decreased blinking – LASIK can decrease tear production and contribute to dry eyes.
- Prolonged use of AC results in greater rate of tear evaporation.
- Environmental conditions. Exposure to smoke, wind and dry climates can increase tear evaporation resulting in dry eye symptoms.
- Heavy makeup may cause contamination of tear film which results into dry eyes.
- Long-term use of contact lenses.
- Systemic autoimmune disease – Sjögren's syndrome, lupus, scleroderma, chronic graft versus-host disease, rheumatoid arthritis.
- Other medical causes – Vitamin A deficiency, Hepatitis C.
- Exogenous factors – radiation therapy, chemical injuries.
- Low intake of omega-3 fatty acids.
- Other factors. Long-term use of contact lenses can be a factor in the development of dry eyes.
- Lagophthalmos – facial nerve palsy, proptosis, vertical lid shortening.
- Ocular autoimmune disease – atopy, cicatricial pemphigoid.

Signs and symptoms of dry eye

Non-specific symptoms such as visual disturbance, photophobia and ocular discomfort, including foreign body sensation, grittiness and burning are often reported by patients. Discomfort may trigger reflex tearing hence there may be paradoxically excessive wateriness. Other unrelated eye conditions such as ocular allergy, corneal erosion and foreign body may also present with these symptoms.

Consequences of dry eye disease

Most people with mild dry eye syndrome have no long-term problems or complications, but severe symptoms can lead to eye inflammation, infection, and damage to the surface of the cornea. Ocular surface complications (i.e., increased susceptibility to irritation, allergy, and infection and reduced antibacterial function, superficial punctuate keratopathy, secondary conjunctivitis/keratitis, and squamous metaplasia of the conjunctiva) may be initiated by instability of the tear film.[8] This damage can lead to ulceration or scarring, which can be painful and affect the patient's vision.

Dry eye diagnosis and evaluation

The suggested sequence of dry eye diagnostic tests is: history and examination followed by a symptom questionnaire; tear break-up time and ocular surface fluorescein staining; Schirmer test; lid and meibomian morphology and meibomian expression.In a Delphi panel, the most frequently cited tests were slit-lamp examination and fluorescein staining (100%) followed by tear breakup time and medical history (both 94%).[9] It is essential to consider local findings like MGD (Meibomian gland dysfunction) and systemic diseases, including autoimmune conditions like Sjögren's, rosacea, chronic overlapping pain, and migraine.[10] It is important to note that new diagnostic tests are needed to evaluate the presence of nerve dysfunction.

Fig. 3 Dry eye diagnosis and evaluation*

Assessment tool	Evaluation
Corneal and conjunctival vital dye staining	Assessment of damage to ocular surface
Meibomian-gland grading	Classification of meibomian-gland dysfunction on the basis of anatomical changes, pathophysiological changes, or disease severity (e.g., plugging of the glands and quality of glandular secretions and meibum)
Schirmer test (with or without anesthesia)	Assessment of tear volume, measured as moisture bsorbed onto paper strips placed inside lower eyelids of both eyes for 5 min
Questionnaires	Patient-reported outcome measures assessing severity of dry eye symptoms, effects on vision-related quality of life, and visual functioning: • Dry Eye Questionnaire • Dry Eye Questionnaire 5 • Ocular Surface Disease Index • National Eye Institute Visual Functioning Questionnaire 25 • Impact of Dry Eye on Everyday Life • McMonnies questionnaire • Symptom Assessment in Dry Eye • Standard Patient Evaluation of Eye Dryness questionnaire • Vision-Targeted Health-Related Quality of Life questionnaire (NIH Toolbox) • Visual-analogue scale
Tear-film stability	Assessment of tear-film breakup time, measured by instilling sodium fluorescein vital dye onto the eye and measuring the time required for dry spots to appear on the corneal surface after blinking (short breakup time is a sign of poor tear-film quality) or by other optical methods
Tear osmolarity	Measurement of solutes in tear fluid (increased levels are seen in dry eye)

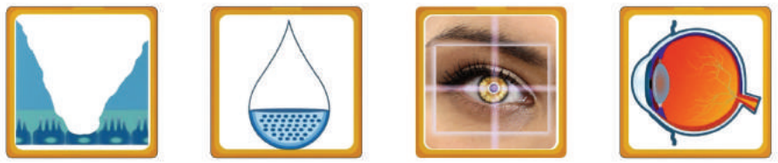
Fig. 3 Dry eye diagnosis and evaluation* *(continued)*

Assessment tool	Evaluation
Tear-film interferometry	Assessment of balance between the lipid and aqueous layers of the tear film (to distinguish clinical subtypes of dry eye)
InflammaDry immunoassay	Measurement of MMP9 levels in the tear film (levels >40 ng/ml indicate ocular surface inflammation)

*MMP9 denotes matrix metalloproteinase 9, and NIH, National Institutes of Health.

Managing dry eyes - Current challenges

Dry eye disease is multifactorial



Needs comprehensive approach... Which goes beyond lubrication!

✓ **Dry eye disease: Multifactorial challenge** - The The TFOS DEWS II® report redefines dry eye as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." There are modifiable and non-modifiable risk factors associated with the mechanisms of dry eye development. The main non-modifiable risk factors are age, female sex, Asian race, Sjögren's syndrome, soft tissue diseases, MGD, androgen deficiency, and the use of certain drugs (e.g., isotretinoin), while modifiable risk factors include intensive computer use, contact lens use, and environmental factors (pollution, low humidity, sick building syndrome, etc).[11]

✓ **Lubricants offer only symptomatic care** - Most lubricating eye drops provide moisture and relief for dry eyes due to temporary causes, like being tired or being in a dry climate by adding some of the same elements that tears naturally have. Tear substitutes are only providing symptomatic relief. The preservatives present in these formulations are also a cause of dry eye, whereas those available without preservatives (e.g., may not be cost-effective).[12]

✓ **Comprehensive care across tear film layer** - Dry eye diagnosis and treatment are evolving. Etiology-oriented treatment has gained importance in the meetings held by ADES (The Asia Dry Eye Society) and TFOS (Tear Film and Ocular Surface Society), and ADES has acknowledged the "**Tear Film Layers-Oriented Therapy**" protocol. The ultimate goal of DED treatment is to restore homeostasis of the ocular surface and tear film by breaking the vicious cycle of the disease. In the majority of DED patients, the general purpose should be to start treatment with the interventions most likely to be beneficial, and use more advanced and specific treatments that target the pathophysiology.[13]

Section II

Softdrops

TREATMENT BEYOND LUBRICATION

Composition

Carboxyoxymethyl cellulose Sodium USP	0.5% w/v
Glycerin BP	0.5% w/v
Stabilized Oxychloro Complex	0.01% w/v
N-Acetyl Carnosine	

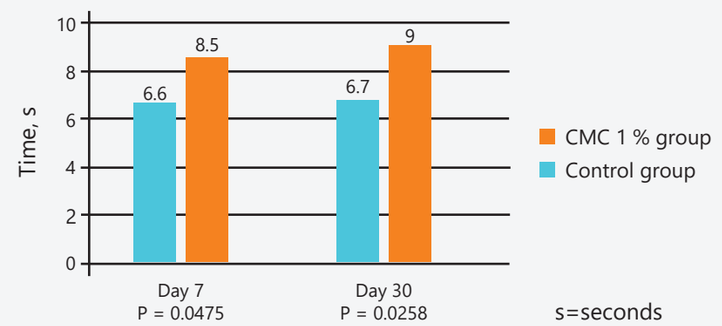
Efficacy studies on components of Softdrops

Carboxymethyl cellulose Sodium USP 0.5% [Tear film retention]

Carboxymethyl cellulose (CMC) is a cellulose derivative often used as its sodium salt, as a lubricant in artificial tears. The properties of CMC which contributes to the lubrication of the eye surface include viscoelasticity. This increases the stability of the pre-corneal tearfilm which, in turn, protects the eye surface against environmental aggressions. Similarly, due to its molecular characteristics as a polysaccharide, CMC exhibits retensive properties which enhances the permanence of the compound and increases the moistening of the eye surface.

In this multicenter, open-label, controlled study, 180 individuals were randomized to conventional therapy treatment with CMC 1% (n=90) or with conventional therapy only (control group, n=90). The efficacy and safety of carboxymethyl cellulose sodium 1% ophthalmic solution in the treatment of signs and symptoms of dry eye was assessed.

Fig. 4 Tear breakup time (TBUT) in CMC vs control group



Tests like the Schirmer test with anesthesia, lissamine green and fluorescein staining , and Tear breakup time (TBUT) were done. Pre-operatively (baseline) and post-operatively at 7 and 30 days, we performed an evaluation using the Ocular Surface Disease Index (OSDI) questionnaire and a patient subjective symptom evaluation.

Results showed that the TBUT was significantly longer in the CMC 1% treatment group compared with the control group at day 7 (8.5 ± 5.5 versus 6.6 ± 3.8s; p=0.0475) and day 30 (9.0 ± 5.9 versus 6.7 ± 4.8s; p=0.0258; Fig. 4).[14] Compared with baseline, TBUT significantly increased in patients in the CMC 1% treatment group ($p<0.001$ at both day 7 and day 30) with a presurgical diagnosis of dry eye, but significantly decreased in patients in the control group ($p<0.02$ at both day 7 and day 30) with no prior diagnosis of dry eye.

Fluorescein and lissamine staining, OSDI questionnaire and subjective symptom scores all improved from baseline, with no significant differences between the two groups. No significant differences in tolerability and safety were observed between the group receiving CMC and conventional therapy, and those receiving conventional therapy only. Treatment with CMC 1% can provide significant improvement in tear film stability.

In a meta-analysis, the efficacy of two artificial tears, carboxymethyl cellulose and hyaluronate (HA), was compared in the treatment of patients with dry eye disease. The efficacy was compared in terms of the mean change from baseline in tear break-up time. The meta-analysis was conducted using both random and fixed effect models. Five studies

were included involving 251 participants. Random effect model meta-analysis showed no significant difference between CMC and HA in treating dry eye disease (pooled standardized mean difference [SMD]=-0.452; 95% confidence interval [CI], -0.911 to 0.007; P=0.053). In contrast, fixed effect model meta-analysis revealed significant improvements in the CMC group when compared to the HA group (pooled SMD=-0.334; 95% CI, -0.588 to -0.081; P=0.010). The efficacy of CMC appeared to be better than that of HA in treating dry eye disease, although meta-analysis results were not statistically significant.[15]

Glycerin BP 0.5% [Tear film maintenance]

Components of the ocular surface synergistically contribute to maintaining and protecting a smooth refractive layer to facilitate the optimal transmission of light. At the air–water interface, the tear film lipid layer (TFLL), a mixture of lipids and proteins, plays a key role in tear surface tension and is important for the physiological hydration of the ocular surface and for ocular homeostasis. Alterations in tear fluid rheology, differences in lipid composition, or down regulation of specific tear proteins are found in most types of ocular surface disease, including dry eye disease (DED).[16]

Carboxymethyl cellulose and glycerol in DED

The efficacy and tolerability of sodium carboxymethyl cellulose (0.5%) and glycerol (0.9%) in patients with keratoconjunctivitis sicca (KCS) was evaluated in this non-interventional and observational study of patients with dry eye who required a change of medication or were naïve to dry eye treatment (N = 5,277).

Disease severity, tear break-up time (TBUT), tolerability, and change in clinical symptoms were recorded at baseline and at final visit (2 to 4 weeks after first treatment). The severity of KCS was mild in 18.6%, moderate in 59.9%, and severe in 21.5% of patients based on physicians' assessment. TBUT was measured in 4,338 patients before switching to or initiating therapy with sodium carboxymethyl cellulose (0.5%) and glycerol (0.9%) and at final visit.

Baseline measurement of mean TBUT was 7.7 ± 3.9 seconds. This value increased to 10.0 ± 4.7 seconds at final visit. Most patients (85.4%) reported improvement in local comfort. The majority (75.1%) of patients felt an improvement in symptoms after changing their treatment.

Two percent of patients reported adverse events, and 0.4% were treatment-related. Sodium carboxymethyl cellulose (0.5%) and glycerol (0.9%) was well tolerated and improved the symptoms of dry eye after 2 to 4 weeks.[17]

N-Acetyl Carnosine (NAC) [Tear film protection]

N-Acetyl Carnosine exerts anti-glycation, bio-activating anti-oxidant properties. N-Acetyl Carnosine is also believed to reduce the build of lactic acid in the ocular tissues, which may otherwise create an environment vulnerable for inciting tear film instability. The anti-oxidant action of NAC is based on scavenging lipid peroxides. It possesses a comprehensive action across lens and cornea by virtue of high bioavailability in ocular tissues. Scientific evidence also indicates that N-Acetyl Carnosine may benefit across multiple ocular conditions like corneal disorders, eye strain, computer vision syndrome and symptoms of dry eye disease.[18]

Stabilized Oxychloro Complex 0.01% [Tear film nourishment]

Stabilized Oxychloro Complex (SOC) is a combination of chlorine dioxide, chlorite and chlorate which causes oxidation of intracellular lipids and glutathione, interrupting vital enzymes for cell function and maintenance. Compared with other preservatives, stabilized oxychloro complex is well tolerated. Physicians should consider treatment with new-generation preparations containing low-risk preservatives such as SOC, especially in patients receiving multiple ophthalmic medications.[19] Stabilized Oxychloro Complex has demonstrated antimicrobial activity against bacteria, viruses and some fungi. Because of its propensity to generate free radicals, it is an effective oxidizer and also breaks down rapidly when exposed to the ocular surface.[20]

Section III

Softdrops EYE DROPS - Comprehensive Care Across All Layers of Tear Film

Carboxymethyl cellulose 0.5% + Glycerin 0.5% + N-Acetyl Carnosine 1%

Carboxymethylcellulose

- Binds to corneal surface increases retention time
- Facilitates corneal healing

Glycerin

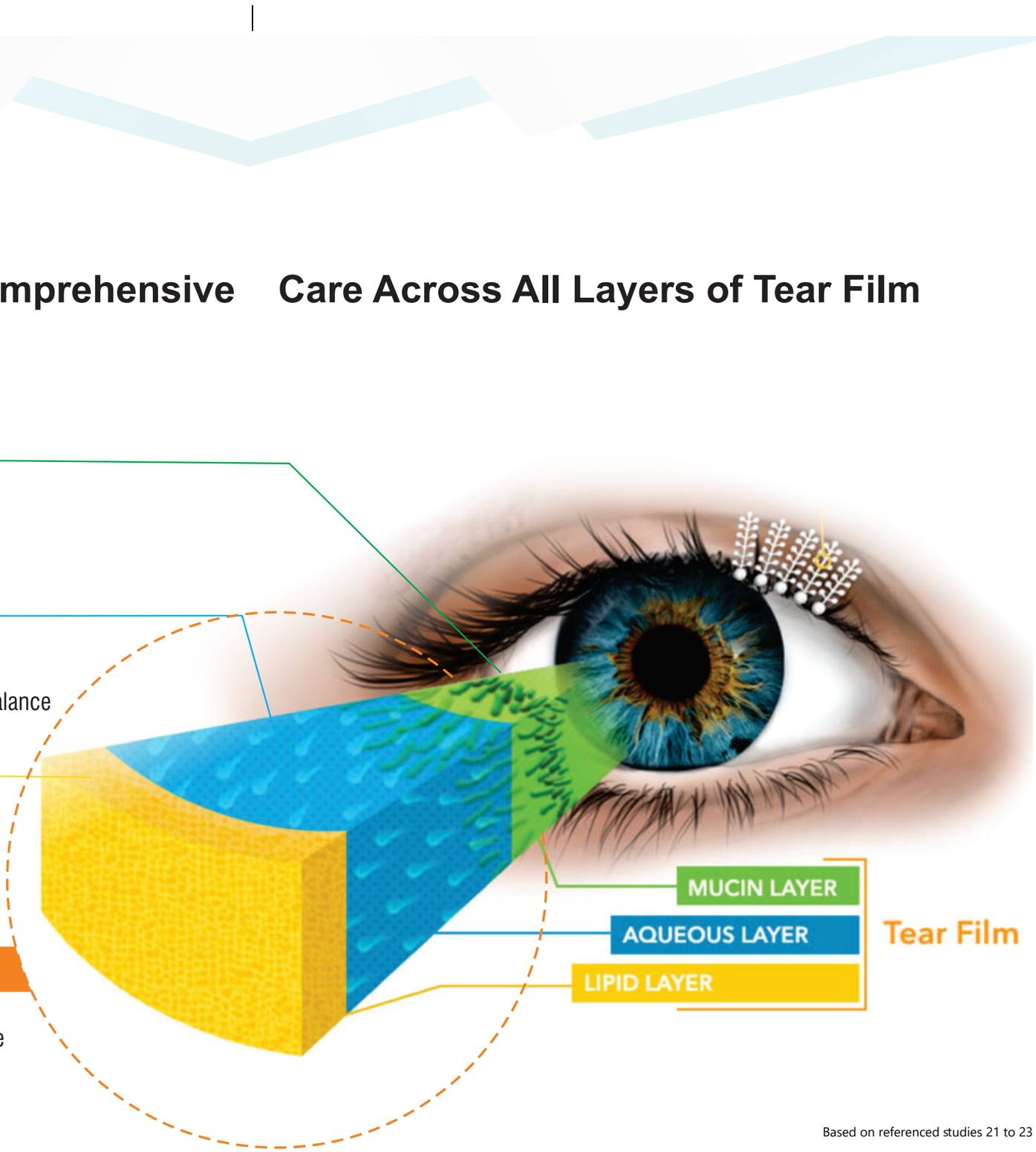
- Rapidly enters ocular surface cells
- Osmoprotection: Helps maintain normal osmotic balance

N-Acetyl-Carnosine

- Anti-oxidant action in lens & cornea
- Scavenger of lipid peroxides

Stabilized Oxychloro Complex

- Releases O2 & H2O & Nourishes the ocular surface
- Anti-microbial properties



Based on referenced studies 21 to 23

Section IV

Softdrops

RESTORES TEAR FILM HOMEOSTASIS

- ✓ Carboxymethyl cellulose Sodium is a derivative of cellulose. Softdrops eye drops contain Carboxymethyl cellulose Sodium and Glycerin, which provides synergistic protection against dry eyes, and other forms of eye irritation including age-related changes. Glycerin and Carboxymethyl cellulose Sodium acts as a demulscents. They moisturize and soothe dry, and irritated eyes.
- ✓ Softdrops also contains the specific antioxidant N-Acetyl Carnosine, which is a free radical scavenger. N-Acetyl Carnosine is a time-release form of the naturally occurring dipeptide L-carnosine — a powerful antioxidant and anti-glycating agent. This form of L-carnosine has access to both the aqueous and lipid portions of the eye and can protect and even repair DNA damage.
- ✓ Softdrops also contains S.O.C (Stabilized Oxychloro Complex) - Chlore derivative composed mainly by Chlorite (NaClO2) and Chlorate-Chlorine. Chlorite acts by producing a high degree of oxidation of glutathione, thus reducing the cell's defenses against oxidative stress. This dissipates into water and sodium chloride-components of natural tears when exposed to ambient light.

Section V

Softdrops

CLINICAL PHARMACOLOGY

Description - Softdrops eye drops contain Carboxymethyl cellulose Sodium and Glycerin, which provides synergistic protection against dry eyes, and other forms of eye irritation including age-related changes. Softdrops also contains the specific antioxidant N-Acetyl Carnosine, which is a free radical scavenger and Stabilized Oxychloro Complex which works comprehensively across tear film & nourishes it.

Indications and dosages - For use as a lubricant and protectant against irritation or to relieve dryness of the eye. Instill 1 or 2 drops in each eye 1 to 4 times a day or as directed by a physician.

Warnings, drug interactions and adverse effects - To avoid contamination, do not touch the tip of container to any surface. Replace the cap immediately after using. Once opened, discard container and any contents after 30-days. Do not freeze. Do not use if seal is broken or if solution changes color or becomes cloudy. Not recommended for children under the age of 12 years. If the eye tissue becomes more inflamed, red, irritated or uncomfortable after using this product, immediately discontinue the use of product and consult an eye-physician if necessary. No interactions have been observed. Rare (>1/10,000, <1/1,000) adverse effects: Irritation/stinging/burning sensation. Very rare (<1/10,000) adverse effects: Allergic reaction, pain, hyperaemia, and conjunctivitis.

Presentation and storage - Available in 10 ml vial. Store at a temperature not exceeding 25°C. Protect from light.

TAKE HOME MESSAGE

✓ Dry eye disease (DED) is a disorder of the tear film characterized by tear deficiency, excessive tear evaporation and unstable tear film, causing a variety of symptoms and/or visual impairments, potentially accompanied by ocular surface damage.

✓ Softdrops provides temporary relief of discomfort due to minor irritations to the eye or exposure to wind or sun. These drops, based on their formulation and active ingredients, are intended to (i) expand tear volume in aqueous tear deficiency; (ii) improve symptoms of dry eye in meibomian gland dysfunction patients; and (iii) enhance the tear film (TF) lipid layer of the TF and therefore improve TF stability and reduce tear evaporation.

✓ Softdrops eye drops contain carboxymethyl cellulose sodium and glycerin, which provide synergistic protection against dry eyes, and other forms of eye irritation including age-related changes. Softdrops also contains the specific antioxidant N-Acetyl Carnosine, which is a free radical scavenger.

✓ Stabilized oxychloro complex (SOC) is well tolerated. Physicians should consider treatment with new-generation preparations containing low-risk preservatives such as SOC because of its antimicrobial activity against bacteria, viruses and some fungi. Also due to its propensity to generate free radicals, it is an effective oxidizer and also breaks down rapidly when exposed to the ocular surface.

✓ Softdrops provides a unique therapeutic option for comprehensive care in dry eye management and helps to restore tear film homeostasis.

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