the dry eye foundation
26273 Twelve Trees Lane NW | Poulsbo Washington 98370 | 1-800-484-0244 | info@dryeyefoundation.org

September 29, 2022

VIA FEDEX EXPRESS AND EMAIL
C. Randall Harrell MD, Chairman & CEO
Regenerative Processing Plant LLC
34176 US Hwy 19 N
Palm Harbor, FL 34684

OPEN LETTER TO REGENERATIVE PROCESSING PLANT LLC
What is in Regener-Eyes Ophthalmic Solution? Is it a biologic?

Dear Dr. Harrell:

The Dry Eye Foundation is a 501(c)(3) nonprofit organization serving the ocular surface disease and ocular surface pain patient communities. We provide platforms for mutual education, support and encouragement across the international community of sufferers, and we advocate for patient-centered research into effective treatment for the multi-factorial conditions collectively referred to as dry eye disease.

Chronic ocular surface pain, often but not always associated with "dry eye", causes profound suffering. Eye pain affects all of our basic daily activities such as working, driving, sleeping, even just taking a walk. It feels relentless and inescapable. It can have a devastating impact on our quality of life. Too often, it spills over into our mental health. Depression, anxiety and suicidal ideation are serious problems in our community(1). And the number of people affected is constantly growing, including in younger populations.

The lived experiences of people with ocular surface pain have transformed dry eye disease from an obscure syndrome associated with auto-immune conditions to today's *five billion dollar global industry*. When the first dry eye drug received FDA approval in 2003, its unexpected blockbuster success prompted badly needed new investments in research and development. But it also attracted companies more interested in profit than verified medical advances. The notorious readiness of severely symptomatic dry eye patients to try anything and pay anything continues to be a magnet for profiteers. We are vulnerable to promises of relief. Sometimes, we overlook warning signals and abandon safety in favor of hope.

Biologic eye drops(2) are a relatively recent innovation, introduced to our dry eye community by the Regenerative Medicine industry. They promise well: they are said to be natural; they are said to help our body heal itself; and they are certainly more convenient to procure and to store than the eye drops manufactured from our own blood which so many of us now use.

As you are probably aware, the Dry Eye Foundation has been running an educational campaign about biologic eye drops on a website dedicated to this purpose(3). We first became concerned about the safety of biologic eye drops upon discovering that they are packaged in an unsafe bottle which offers no protection against bacterial contamination(4). We opened a dialogue with the Food and Drug Administration. As our research progressed, more safety red flags emerged, ranging from demonstrably false claims about regulatory compliance status to reports we have received from our community of adverse events. Our worries have been augmented by reading the detailed findings in recent FDA Warning Letters sent to two noncompliant manufacturers of two biologic eye drops(7,8).

For Regener-Eyes, our first safety concern is very simple: *we don't know what it is*.

What is in Regener-Eyes?

There is no Ingredient List on the Regener-Eyes bottle, package, insert (Attachments 1,2,3) or website(9).

Regener-Eyes LLC sales representatives refuse to answer questions about ingredients, even when asked by patients who are concerned because they have ingredient allergies or sensitivities(10).

DailyMed (National Library of Medicine) is the recognized drug label database where the ingredients of prescription and over-the-counter medications may be found. According to DailyMed(11,12), Regener-Eyes' *active* ingredient is **glycerin** (0.4% for Lite and 0.5% for Pro), and it has two *inactive* ingredients: **"Tonicity Solution™"** and **sterile water.**

In our organization's interactions with patients and providers, no one has seemed aware that Regener-Eyes might contain glycerin (common enough in OTC eye drops) let alone that it might be *the* active ingredient.

Tonicity Solution™ does not have a Unique Product Identifier (UNII) or any references. We cannot determine what it is without your cooperation.

Is Regener-Eyes "biologic"?

Patients pay $75 to $175 or more for a single 3 mL vial of Regener-Eyes because they believe it to be an all-natural biologic eye drop.

Regener-Eyes has always been known as a biologic. Its marketing tagline, until quite recently, was "The power of a biologic in the ease of an eyedrop"(13). Key Opinion Leaders in optometry and ophthalmology uniformly describe Regener-Eyes as a biologic in trade journals(14,15,16,17,18,19). A White Paper sponsored by Regener-Eyes LLC and published in the July 2021 issue of Eyeworld describes Regener-Eyes as a biological product(Attachment 4).

In August 2022, Regener-Eyes LLC stopped describing Regener-Eyes as biologic. All obvious references to biologic substances have been removed from regenereyes.com and from the social media accounts of Regener-Eyes LLC and its employees. Regener-Eyes LLC's product brochure(Attachment 5), distributed to visitors at a recent national trade show, contradicts the White Paper about what Regener-Eyes is and what it does(20).

In the meantime, doctors continue to recommend Regener-Eyes as a biologic, often quoting content originating from regenereyes.com before it was scrubbed of biologic references(21,22,23,24), and distributors continue to advertise Regener-Eyes to physicians(25) and consumers(26) as a biologic.

If Regener-Eyes is biologic, what is its tissue or fluid of origin?

Your website, which currently states that Regener-Eyes' ingredients are "proprietary", previously stated that it was derived from **placenta**.(27) The White Paper states that Regener-Eyes is derived from **placental biomaterials** (Attachment 4).

According to DailyMed archives, from October 2021 to August 2022, Regener-Eyes was stated to contain the *active* ingredient glycerin and the *inactive* ingredients **"d-MAPPS"** and 0.9% Sodium Chloride USP(28,29). "d-MAPPS" does not have a Unique Ingredient Identifier (UNII) and cannot be found in any ingredient database. According to your 2022 study in Analytical Cellular Pathology(30), d-MAPPS is a biological substance; its origin is not specified. Your 2019 study in Current Stem Cell Research & Therapy(31) reports that d-MAPPS is derived from **amniotic fluid**. A 2018 publication in Clinical Ophthalmology(32) reports that Regener-Eyes is made from **amniotic fluid**.

We patients need to know what we're putting in our eyes.

Drug ingredients are basic information. There is no legitimate reason to conceal ingredients. The Federal Code of Regulations requires this information to be provided for all prescription and over-the-counter medications(33).

The Dry Eye Foundation eagerly anticipates a definitive resolution to the question of what is in Regener-Eyes.

Sincerely,

Rebecca Petris
President

NOTES

1) https://www.mydryeyedata.org/qol-list/emotions
2) https://www.biologiceyedrops.org/faq
3) https://www.biologiceyedrops.org
4) https://www.biologiceyedrops.org/watch/preservative-free-eye-drops
5) https://www.biologiceyedrops.org/fda-weighs-in
6) https://www.biologiceyedrops.org/fiction-or-fact
7) https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/vitti-labs-llc-627699-07282022
8) https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/biolab-sciences-inc-621465-08232022
9) "Each product is created using 100% natural, patented, proprietary ingredients and is preservative-free." https://www.regenereyes.com/our-products/
10) Verbal and email reports by patients and eye care providers to Dry Eye Foundation; conversations between Dry Eye Foundation volunteers and Regener-Eyes telephone representatives.
11) https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=e689001a-3640-1d45-e053-2995a90a4032&type=display
12) https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=e689001a-3640-1d45-e053-2995a90a4032&type=display
13) https://web.archive.org/web/20220000000000*/regenereyes.com
14) https://www.reviewofoptometry.com/article/new-options-front-to-back
15) https://www.ophthalmologymanagement.com/issues/2021/march-2021/rx-perspective
16) https://www.ophthalmologymanagement.com/issues/2022/january-2022/quick-hits
17) https://www.reviewofcontactlenses.com/article/from-basics-to-biologics-selecting-drops-for-every-dry-eye-patient
18) https://www.optometrytimes.com/view/therapy-options-based-on-ded-severity
19) https://www.optometricmanagement.com/issues/2021/july-2021/focus
20) https://www.biologiceyedrops.org/watch/which-one-is-it-regener-eyes
21) https://www.bheyeguy.com/blog/regener-eyes-biologic-eye-drop
22) https://www.docnanda.com/regenereyes
23) https://beyereye.com/about-regener-eyes/
24) https://www.ocdryeye.com/body
25) https://www.abboptical.com/regener-eyes-lite
26) https://dryeyerescue.com/collections/regener-eyes
27) See FAQ, "What are Regener-Eyes Ophthalmic Solutions Made of", https://web.archive.org/web/20220119223552/https://www.regenereyes.com/dosage-and-faqs/
28) https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=667753
29) https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=667757
30) https://www.hindawi.com/journals/acp/2022/3655595/
31) https://www.regenereyes.com/wp-content/uploads/2021/05/Therapeutic-Potential-of-Amniotic-Fluid-Derived-Mesenchymal-Stem-Cells-Based-on-their-Differentiation-Capacity-and-Immunomodulatory-Properties.pdf
32) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6012548/
33) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-349

ATTACHMENTS

1) Regener-Eyes bottle
2) Regener-Eyes package
3) Regener-Eyes package insert
4) Therapeutic Potential of Regener-Eyes Ophthalmic Solution (Eyeworld supplement, June 2021)
5) Regener-Eyes product brochure (Vision Expo West, September 2022)

COPIES TO:

1. Food and Drug Administration
CDER / Office of Unapproved Drugs and Labeling Compliance
CBER / Director (Peter Marks, MD, PhD)
CBER / Office of Regulatory Operations (Christopher Joneckis, PhD)
CBER / Office of Compliance and Biologics Quality (Melissa Mendoza, JD)
CBER / Office of Biological Products Operations, Division 2 (Karlton Watson)
CBER / Office of Biological Products Operations, Division 1 (Elizabeth Waltrip)
CBER / Office of Product Jurisdiction (Sheryl Lard-Whiteford, PhD)

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Eric Donnenfeld MD
Marguerite McDonald MD
Sandra Cremers MD
Paul Karpecki OD
Walt Whitley OD
Ahmad Fahmy OD
Walter Choate OD
James Thimons OD

3. Scientific Advisory Board of Regener-Eyes LLC
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Prof. Vladislav Volarevic
Malcolm Maden PhD
Jeremy Mao DDS PhD

4. Additional organizations:
Sjogrens Foundation
Prevent Blindness
Scleral Lens Education Society

5. Dry Eye Foundation Board of Directors


Processed by:
Regenerative Processing Plant, LLC
(Palm Harbor, FL) 727-781-0818
Professional Strength
Regener-Eyes®
OPHTHALMIC SOLUTION
"A drop of relief"
Sterile
Moisturizing Eye Drops
Store Refrigerated
Contains No
Preservative
Single Patient Use Only
See enclosed insert for
"Instructions For Use"
Professional Strength
Regener-Eyes®
OPHTHALMIC SOLUTION
"A drop of relief"
Sterile
Moisturizing Eye Drops
Store Refrigerated
Contains No
Preservative
Single Patient Use Only
See enclosed insert for
"Instructions For Use"
Regenerative
Processing
Plant, LLC
6176 US Highway 19 N
Palm Harbor, FL 34684
(800) 781-0818
DESCRIPTION: REGENER-EYES®
Ophthalmic Solution
SIZE/VOLUME: 3.0ml
Exp:
8/26/2024
082821-052


Regener-Eyes®
OPHTHALMIC SOLUTION
LITE
"A drop of relief"
STERILE
MOISTURIZING
EYE DROPS
Store at
Room Temperature
Contains No
Preservative
Single Patient Use Only
See enclosed insert for
"Instructions For Use"
Regener-Eyes®
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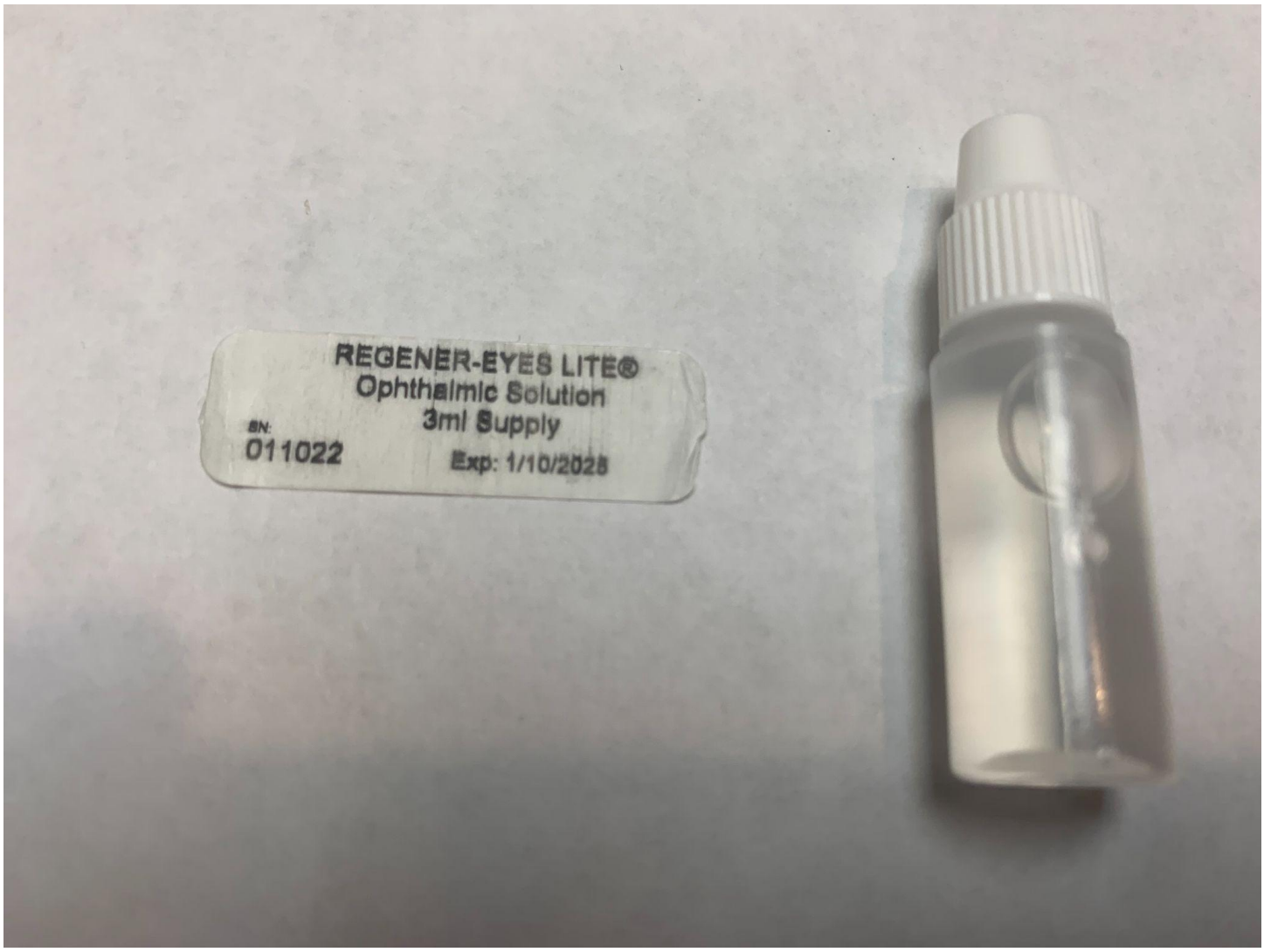
Single Patient Use Only
See enclosed insert for
"Instructions For Use"
Regenerative
Processing
Plant, LLC
34176 US Highway 19 N
Palm Harbor, FL 34684
(800) 781-0818
PRODUCT CODE: REG-LT
DESCRIPTION: REGENER-EYES LITE®
Ophthalmic Solution
SIZE/VOLUME: 3.0cc
011022-734


REGENER-EYES LITE®
Ophthalmic Solution
3ml Supply
SN:
011022
Exp: 1/10/2028

GENERAL DESCRIPTION

RegenerEyes® Ophthalmic Solution is a versatile and convenient biologic in eye drop form.

RegenerEyes® Ophthalmic Solution should be discussed with your vision professional prior to use.

- **RegenerEyes® Ophthalmic Solution** is a sterile solution packaged in a 3 ml bottle.
- **RegenerEyes® Ophthalmic Solution** is distributed exclusively by qualified vision health care professionals (e.g., Ophthalmologists, Optometrists, etc.).
- **RegenerEyes® Ophthalmic Solution** is processed using sterile techniques and provided sterile by means of Regenerative Processing Plant, LLC's (**RPP**) patent protected process.
- **RPP** assumes no responsibility for the clinical use of this product.

STORAGE INSTRUCTIONS AND CONDITIONS

It is recommended that **RegenerEyes® Ophthalmic Solution** be maintained in a refrigerated state at 2°- 8° C once received.

INSTRUCTIONS FOR USE

1. Remove package from refrigerator.
2. Shake the dropper to mix the ingredients.
3. To open, hold the bottom of the vial securely and twist the top. Remove top.
4. Wash your hands, tilt head back, lift upper eye lid with finger and position the dropper as close to the eye as possible being careful not to touch the vial tip to eye tissues.
5. Apply **1 drop** of **RegenerEyes® Ophthalmic Solution** in each eye. Or as your doctor has recommended.
6. Return remaining product to the refrigerator. Wash hands.
7. Reapply as directed.

DONOR SCREENING AND TESTING

Prior to processing, the donor is screened for conditions or disease processes that would contraindicate the donation of tissue in accordance with current policies and procedures by an FDA registered tissue bank. All policies and procedures for donor screening, serologic, and microbiologic testing meet current regulations established by the FDA and other state and local governing bodies. Contraindications for tissue donation include: presence of infectious disease, neurological degenerative disease, disease of unknown etiology, and exposure to toxic substances. The donor is also screened for HIV, hepatitis, and other relevant communicable disease agents in accordance with current United States Public Health Services Recommendations and FDA Federal Regulations and Guidance Documents.

Communicable disease testing has been performed by a laboratory registered with the FDA to perform donor testing and certified to perform such testing on human specimens in accordance with Clinical Laboratory Improvement Amendments (CLIA) and 42 CFR Part 493, or that has equivalent requirements as determined by the Centers for Medicare and Medicaid Services. Names and addresses of testing laboratories, interpretation of all required infectious disease tests, and a listing of the documents reviewed as part of the relevant medical records are kept on file at the processing tissue bank.

Donor blood samples taken prior to or at the time of recovery were tested by laboratories certified under the CLIA and were found negative using FDA licensed tests for, at minimum:

- **HBsAg: Hepatitis B Surface Antigen**
- **HBcAb: Hepatitis B Core Antibody**
- **HCVAb: Hepatitis C Antibody**
- **HIV 1/2/Ab: Human Immunodeficiency Virus Types 1/2 and O Antibody**
- **HCV NAT: Hepatitis C Virus**
- **HIV NAT: Human Immunodeficiency Virus**
- **HBV NAT: Hepatitis B Virus**
- **RPR/STS or Equivalent: Syphilis**
- **WNV: West Nile Virus**

PROCESSING AND STERILITY

Donor biomaterials are recovered using the safest recovery techniques and sterile equipment to minimize any bio burden contamination. **RPP** biomaterials are procured via a network of qualified and trained recovery partners, one of the most stringent screening and recovery protocols, and a highly controlled processing environment, thus countering the risks of disease transmission at every step. All biomaterials are processed sterile utilizing **RPP's** proprietary patent protected process.

ADVERSE REACTION

There have been no reported adverse reactions associated with **Regener-Eyes Lite ®**, however general risks and complications may include, but are not limited to infection and bleeding. Any adverse reaction that may be related to the use of **Regener-Eyes Lite ®** should be reported immediately to **RPP's** Customer Service department at (800) 781-0818.

WARNINGS AND PRECAUTIONS

Regener-Eyes Lite ®:

- If mishandling has caused possible damage or contamination, or the product is past its expiration date
- If any of the allograft elements, packaging, labels, and/or barcodes are missing, damaged, illegible, or defaced
- If it has not been stored according to specifications set forth in this insert

Notify **RPP** immediately if any of the aforementioned conditions exist or are suspected.

TRACKING

Regulations and tracking are outlined for the final disposition, **RPP** provides a Tissue Tracking Record (TTR) with every box of **Regener-Eyes Lite ®**. In order for the consignee to comply, they must complete the pre-printed TTR by recording the information requested. **RPP** has supplied pre-printed labels and a HIPAA compliant self-mailer for easy submission. TTRs must be returned to the processor within 15 days following transplantation. Discarded **Regener-Eyes Lite ®** is NOT exempt from TTR compliance.

Ingredients:

Sterile Ophthalmic Solution

Sterile Water

RETURN POLICY

RPP does not accept the return of **Regener-Eyes Lite ®** products unless it is received damaged or defective. If you experience a problem with your product, notify **RPP** immediately for a Returned Material Authorization (RMA) number at (800) 781-0818.

ELIGIBILITY DETERMINED, PROCESSED, AND DISTRIBUTED BY:

Regenerative Processing Plant, LLC	**Regenerative Processing Plant, LLC** **34176 US HWY 19N** **Palm Harbor, FL 34684** **1 800 781 0818**

PACKAGE DEFINITIONS

STERILE A	Processed for sterility by Regenerative Processing Plant's patent protected processes.
LOT	Lot Number
SN	Fluid Identifying Number (Serial Number)
	Single patient use only
Rx ONLY	Prescription required to order
	See Package Insert Instructions for Use

Rev. 3/2021

ASCRS
EYEWORLD WHITE PAPER

Therapeutic potential of Regener-Eyes® Ophthalmic Solution in the treatment of dry eye disease

by Marguerite McDonald, MD, clinical professor of ophthalmology, NYU Langone Medical Center, New York, New York; clinical professor of ophthalmology, Tulane University Health Sciences Center, New Orleans, Louisiana; cornea/cataract/refractive surgeon and director of the dry eye center of excellence, OCLI Vision, Oceanside, New York; and Carl Randall Harrell, MD, Regenerative Processing Plant, Palm Harbor, Florida

Abstract

Dry eye disease (DED) is a common and multifactorial disease of the ocular surface characterized by a deficiency in quality and/or quantity of the tear fluid. A detrimental immune response has an important role in the development and progression of DED. Dr. Harrell recently developed Regener-Eyes® (generic name "derived-Multiple Allogeneic Proteins Paracrine Signaling [d-MAPPS]"), an ophthalmic solution that contains a large number of immunoregulatory factors that are capable of penetrating the ocular surface and to efficiently attenuate the detrimental immune response in the eye, promoting repair and regeneration of injured tissue. Regener-Eyes® efficiently alleviated DED-related symptoms (dryness, grittiness, scratchiness, soreness, irritation, burning, watering, foreign body sensation, eye fatigue) and improved functional visual acuity in 131 DED patients, without causing any side effects.[12] Herewith, we described in detail the molecular mechanisms and signaling pathways that are responsible for the immunomodulatory effects of Regener-Eyes®, thereby exploring the therapeutic potential of Regener-Eyes® in the treatment of DED.

Introduction

Dry eye disease (DED) is a common and multifactorial inflammatory disease of the ocular surface characterized by a deficiency in quality and/or quantity of the tear fluid.[1] The multifactorial nature of DED involves several interrelated underlying pathologies, including the loss of homeostasis, instability and hyperosmolarity of the tears, and chronic eye inflammation that leads to the neurosensory dysfunction and visual disturbance. Accordingly, DED is usually manifested by dryness, grittiness, scratchiness, soreness, irritation, burning, watering, foreign body sensation, eye fatigue, and reduced functional visual acuity. Significantly impaired performance of vision dependent daily activities (reading, writing, driving) often diminishes the quality of life of DED patients.[2]

A detrimental immune response has played a crucially important role in the development and progression of DED. Accordingly, DED-related symptoms are often observed in patients who suffer from chronic inflammatory and systemic autoimmune diseases (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus).[3–7] Considering the important role of inflammation in DED development, the main treatment strategy has shifted from hydration and lubrication of the dry ocular surface to the immunoregulation-based therapeutic approach, which is designed to break the vicious cycle of

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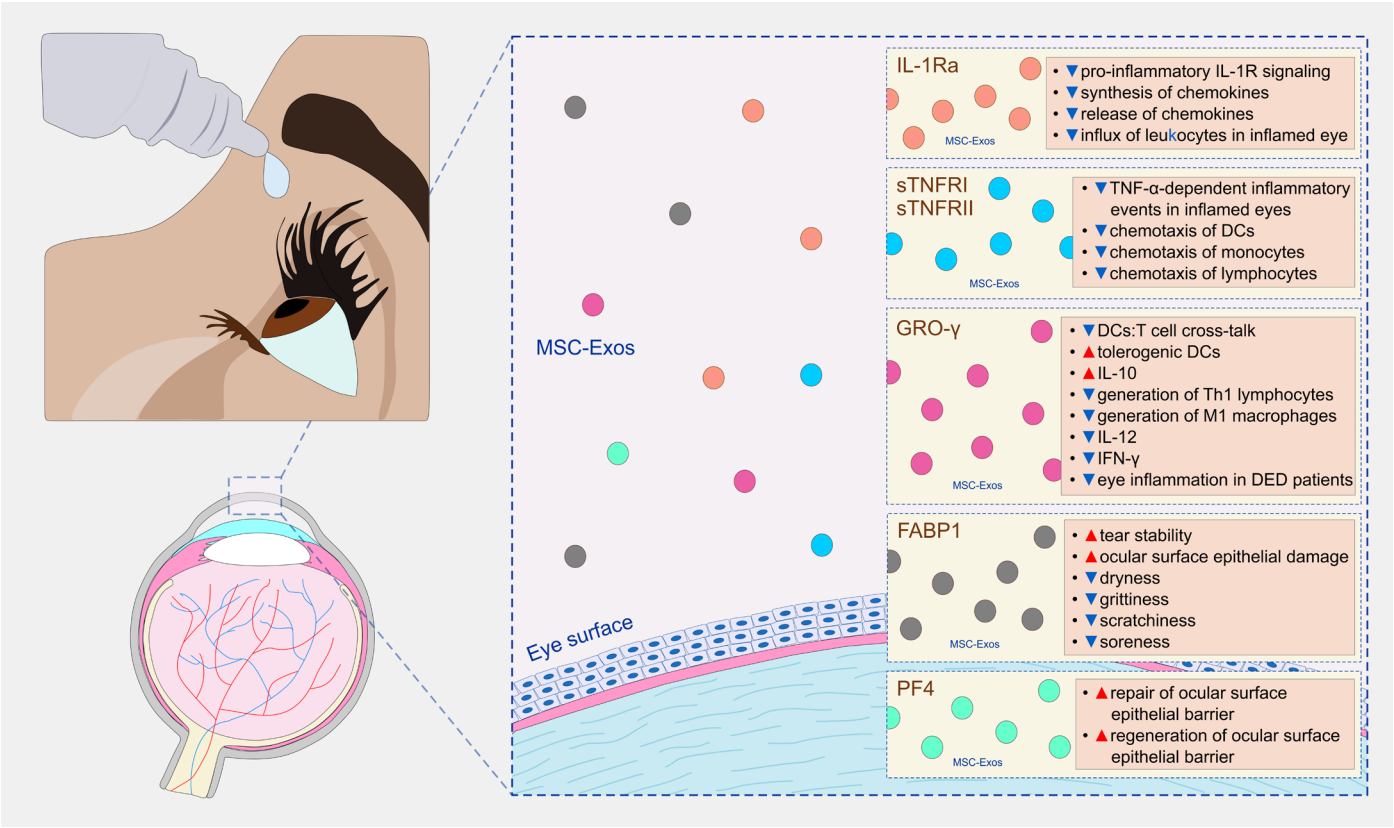
chronic inflammation in the eye.[3–6] The administration of immunosuppressive eye drops has the potential to attenuate the ongoing inflammation, resulting in the alleviation, as the well-developed protective mechanisms of the ocular surface ensure their rapid clearance from the pre-corneal tear film, thus limiting ocular penetration of the drug.[8] Therefore, there is a large unmet need for the development and clinical use of eye drops containing immunomodulatory factors that are able to bypass the ocular surface barrier and reach the target cells of the ocular surface and lacrimal system.[8]

In line with these findings, Dr. Harrell recently developed Regener-Eyes® (generic name "derived-Multiple Allogeneic Proteins Paracrine Signaling [d-MAPPS]"), an ophthalmic solution that contains a large number of immunoregulatory factors that are capable of penetrating the ocular surface to efficiently attenuate the eye's detrimental immune response, which may help to promote the repair and regeneration of damaged corneal tissue.[9] Herein, we described in detail the molecular mechanisms and signaling pathways that are responsible for the immunomodulatory effects of Regener-Eyes®, exploring the therapeutic potential of Regener-Eyes® in the treatment of DED.

Molecular mechanisms responsible for beneficial effects of Regener-Eyes® in DED treatment

Although Regener-Eyes® is acellular, it contains proteins, cytokines in addition to the water, glucose, lactates and electrolytes, and placental-derived biomaterials, which produce a large number of bioactive factors (lipids, proteins, enzymes, cytokines, chemokines, immunoregulatory proteins, trophic and growth factors), as well as microRNAs (miRNAs), which, due to their trophic and antimicrobial properties, support normal fetal growth and offer protection against pathogens and toxins.[10] Additionally, these placental biomaterials contain AF-MSC-sourced exosomes (AF-MSC-Exos), nano-sized extracellular vesicles that are enriched with AF-MSC-derived immunosuppressive molecules and growth factors.[10–11] Due to their nano-sized dimensions and lipid envelope, AF-MSC-Exos avoid biological barriers, and easily penetrate through the lipid-containing cell membranes of the ocular surface through direct fusion with the plasma membrane, thereby delivering their content to the cytosol of target cells.[10–12]

Regener-Eyes® is an engineered biological product derived from human placental-based biomaterials, manufactured under current Good Manufacturing Practices (cGMP), regulated and reviewed by the Food and Drug Administration (FDA).[9] Regener-Eyes® incorporates Regenerative Processing Plant's (RPP) proprietary patented sterilization process to provide for a safe, sterile product for clinical use.[9] Regener-Eyes® is enriched with AF-MSC-Exos containing AF-MSC-derived immunoregulatory, angio-modulatory and trophic factors capable of bypassing biological barriers to efficiently attenuate ongoing inflammation, promoting enhanced tissue repair and regeneration.[8] Specifically, Regener-Eyes® contains interleukin 1 receptor antagonist (IL-1Ra), soluble receptors of tumor necrosis factor alpha (sTNFRI, sTNFRII), growth-related oncogene gamma (GRO-γ), fatty acid-binding protein 1 (FABP1) and platelet factor 4 (PF4), which alleviate eye inflammation, support tear



Molecular mechanisms responsible for beneficial effects of Regener-Eyes®-containing eye drops in the management of DED. Regener-Eyes® contains a large number of immunoregulatory molecules, trophic and growth factors that attenuate ongoing inflammation and may help to promote repair and regenerate the epithelial barrier at the ocular surface of patients suffering from dry eye disease (DED). By delivering immunoregulatory molecules (interleukin 1 receptor antagonist [IL-1Ra], soluble TNF receptors [sTNFRI, sTNFRII], growth-related oncogene gamma [GRO-γ]), Regener-Eyes® inhibits detrimental immune response in inflamed eyes of DED patients, while, by delivering growth and trophic factors (fatty acid-binding protein [FABPI] and platelet factor 4 [PF4]), Regener-Eyes® supports tear stability and prevents injury of epithelial cells. This may contribute to the enhanced repair and regeneration of the epithelial barrier at the ocular surface of DED patients.
Source: Regener-Eyes®

stability, and prevent ocular surface epithelial damage, contributing to the enhanced repair and regeneration of ocular surface epithelial barrier in DED patients.[1,9,11–13]

IL-1Ra is a naturally occurring cytokine that acts as an inhibitor of inflammatory cytokine IL-1β that has a crucially important role in the recruitment of circulating leukocytes in inflamed eyes of DED patients.[5–6,12,14] Alterations in tear production and composition, particularly elevated osmolarity, activates c-Jun N-terminal kinase and NF-kβ signaling pathways in the epithelial cells of DED patients, which result in enhanced secretion of pro-inflammatory cytokine IL-1β.[11] IL-1β induces enhanced expression of adhesion molecules on endothelial cells, enabling the massive influx of antigen-presenting dendritic cells (DCs), macrophages and circulating lymphocytes in the lacrimal glands and ocular surfaces of DED patients.[5–6,12,15] When Regener-Eyes® containing IL-1Ra binds to the IL-1 receptor

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(IL-1R) on the endothelial cells of the eyes of DED patients, binding of IL-1β to IL-1R is blocked and the pro-inflammatory signals from IL-1R are stopped. Accordingly, various pro-inflammatory events, initiated by IL-1β:IL-1R binding, including the synthesis and releases of chemokines and the enhanced influx of leukocytes in inflamed eyes, are inhibited by Regener-Eyes® containing IL-1Ra.[1,9,15]

IL-1β acts synergistically with TNF-α to induce the enhanced recruitment of monocytes and lymphocytes in inflamed lacrimal glands and eyes of DED patients.[5–6] The binding of TNF-α to TNF-α receptors on endothelial cells attract circulating DCs, monocytes and lymphocytes, thereby creating an inflammatory loop within inflamed eyes.[5–6] Regener-Eyes® contains sTNFRI and sTNFRII, which bind to TNF-α and prevent TNF-α-dependent recruitment of circulating inflammatory immune cells in the eyes of DED patients.[1,9]

Cross-talk between IL-1β and TNF-α-recruited DCs, T cells, and macrophages on the ocular surface and inflamed lymph nodes is crucially important for the development and progression of DED.[4–5] DCs capture antigens and present them to the naive CD4+ T cells in regional lymph nodes. DCs, through the secretion of IL-12, induce differentiation of naive CD4+ T cells in effector, IFN-γ-producing Th1 cells, which, in turn, in an IFN-γ-dependent manner, promote polarization of resident macrophages in the inflammatory M1 phenotype.[5] In the eyes of DED patients, inflammatory (M1) macrophages produce large amounts of TNF-α, nitric oxide, and matrix metalloproteinases, which disrupt the epithelial barrier of the ocular surface.[5–6] Regener-Eyes® significantly attenuates the concentration of IL-12 in the supernatants of activated human peripheral blood mononuclear cells (pbMNCs) and alleviates production of IFN-γ in activated lymphocytes.[15] Regener-Eyes® contains GRO-γ, which is able to suppress DCs:T cell cross-talk and efficiently inhibits the DC-dependent generation of inflammatory Th1 cells.[9,15] GRO-γ-treated DCs had a tolerogenic phenotype characterized by increased secretion of immunosuppressive IL-10, and reduced production of inflammatory cytokines IL-12 and IFN-γ.[16] Accordingly, it is expected that topical administration of Regener-Eyes® affects the cross-talk between antigen-presenting, IL-12-producing DCs and naive CD4+ T cells in lymph nodes, thereby preventing DC-dependent generation of IFN-γ-producing Th1 lymphocytes. Since IFN-γ-producing Th1 lymphocytes enhance the inflammatory properties of macrophages and induce their polarization in pro-inflammatory (M1) cells, by delivering GRO-γ, Regener-Eyes® may prevent Th1 cell-dependent activation of intraocular M1 macrophages and attenuates M1 macrophage-driven eye inflammation in DED patients.[1,9,15]

Downregulated levels of FABP proteins were noticed in the tears of patients suffering from Sjögren's syndrome and DED.[17] FABP proteins regulate transepithelial water transport and maintain the epithelial barrier at the ocular surface.[17] Accordingly, the reduced expression and production of FABP proteins leads to disturbances in the epithelial barrier, causing increased tear evaporation and DED.[17] Regener-Eyes® contains a high concentration of FABP1 proteins, which are thought to regulate transepithelial water transport, support tear stability, and prevent ocular surface epithelial damage in the eyes of DED patients, resulting in the possible

alleviation of dryness, grittiness, scratchiness, and soreness.[1,9,17]

A topical administration of platelet-rich plasma eye drops that contains a large amount of PF4, epithelial growth factors, fibroblast growth factors, and vascular endothelial growth factor successfully treated moderate to severe DED. Regener-Eyes® contains a high concentration of PF4, which may promote the repair and regeneration of injured epithelial cells on the ocular surface.[1,9,18] Therefore, the beneficial effects of Regener-Eyes® may be partially explained by the regenerative and protective properties of PF4.[1,9]

Experimental and clinical evidence of Regener-Eyes®-based efficacy in DED treatment

We recently demonstrated that Regener-Eyes® may protect corneal epithelial cells from chemical injury.[12] While cytoplasm vacuolization and swelling, accompanied by the loss of cell-to-cell contact, were observed in benzalkonium chloride (BAC)-treated human corneal epithelial cells (HCEC) in vitro, these morphological and functional changes were not seen in BAC-treated HCEC that grew in the presence of Regener-Eyes®.[12] Additionally, Regener-Eyes® significantly improved viability of BAC-injured HCEC while protecting them from BAC-induced chemical injury.[12]

In line with these results are findings obtained in clinical settings.[12] Regener-Eyes® was shown to help efficiently alleviate ocular discomfort and pain in a study of 131 DED patients (27 males and 104 females with a median age of 62 years [range 19–85]) during a 12-month follow-up period.[12]

Decreases in VAS and SPEED scores in the Regener-Eyes®-treated DED patients were documented 3 months after the administration of Regener-Eyes®, while the highest reduction in VAS and SPEED scores in these patients were observed after 12 months of Regener-Eyes®-based therapy, indicating the increasingly beneficial effects of long-term use in alleviation of ocular symptoms in DED patients.[12] Importantly, Regener-Eyes® was well tolerated. None of 131 Regener-Eyes®-treated DED patients reported any side effects related to the Regener-Eyes® therapy, suggesting that topical application of Regener-Eyes® is a safe and effective therapeutic approach in DED treatment.[12]

Dry eye cases treated with Regener-Eyes®

(Courtesy of Marguerite McDonald, MD)

Case #1, M.R.

A 26-year-old female nurse presented 4 years ago with severe dry eye and epithelial basement membrane disease (EBMD) with recurrent erosion syndrome OU. She has undergone PTKs OU (2017 and 2019, respectively), though symptoms have returned, as new areas of EBMD have appeared outside the prior PTK treatment zones. She is reluctant to have more laser surgery, as she has already lost a lot of time to recurrent erosion episodes and fears the additional downtime will put her job at risk.

M.R. had a best corrected VA of 20/25 –2 OD and 20/30 –2 OS. After being on Regener-Eyes® Professional Strength QID OU for 4 weeks, her best corrected vision improved to 20/20 OU, and she has had

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no recurrent erosion symptoms. M.R. has now been on Regener-Eyes® Professional Strength for 4 months and is symptom-free.

Case #2, S.P.

A 46-year-old male with Sjögren's syndrome presented with extreme pain in both eyes and blurred vision. He was taking cyclosporine emulsion BID OU, preservative-free tears q 1 hour while awake OU, serum tears q 2 hours while awake, bland nighttime ointments OU, and omega-3 nutritional supplements, with minimal relief.

S.P.'s best corrected visual acuity was 20/100 OD and 20/70 OS. His most remarkable findings on slit lamp exam were 4+ corneal filaments OD, 2+–4+ OS, and a markedly decreased tear meniscus OU. His tear osmolarity readings were 391 mOsm/L OD and 359 OS.

Regener-Eyes® Professional Strength QID OU was added to the above regimen, with the exception of serum tears, which he was advised to discontinue. S.P. returned after 1 month with a best corrected visual acuity of 20/50 OD and 20/40 OS, with 2+ filaments OD and 1+–2+ OS. His pain is much improved. He is continuing his current regimen and will return in 2 months.

Case #3, T.R.

A 64-year-old female with a long history of Sjögren's syndrome presented with a non-healing epithelial defect OS. She had been given a course of valacyclovir 1 gram PO TID X 10 days, as well as Zirgan gel (ganciclovir, Bausch + Lomb) 5 X a day OS for 10 days, with no improvement. An amniotic membrane had been inserted but was immediately removed due to the patient's significant pain. T.R. was taking preservative-free tears q 2 hours while awake OU and bland ointment OU at night. On presentation, her best corrected acuities were 20/30 OD and 20/40 OS. A slit lamp exam revealed a 3 X 5 mm epithelial defect in the mid-peripheral cornea OS, in the supertemporal quadrant at 2 o'clock.

Regener-Eyes® Professional Strength QID OU was begun; preservative-free tears q 2 hours while awake OU and bland ointment QHS OU were continued.

On T.R.'s next visit 1 week later, the epithelial defect was healed for the first time in 4 months. The current regimen was continued.

Meibomian gland dysfunction (MGD)/meibomian gland regeneration (MGR)

Meibomian gland dropout and altered meibum secretion were usually seen in the patients suffering from DED.[19–20] Both congenital and acquired meibomian gland dysfunction (MGD) results in increased tear film osmolarity and leads to the development of evaporative DED.[19–20] We recently demonstrated the beneficial effects of Regener-Eyes® in the treatment of MGD-related DED.[13] In one case report, Regener-Eyes® promoted regeneration of injured meibomian glands and efficiently attenuated DED-related symptoms in a patient suffering from MGD.[13] Before the topical application of Regener-Eyes®, the meibomian ducts of this MGD patient were dilated, exhibiting enlargement and

tortuosity.[13] The morphology of the meibomian glands was significantly improved after 3 weeks of Regener-Eyes® therapy showing the hypo-illuminescent grape-like clusters. Similarly, hyper-illuminescent ducts tarsus indicated beneficial effects of Regener-Eyes® in restoration of meibomian gland and ducts morphology.[13] Additionally, Regener-Eyes® significantly improved DED-related symptoms in this MGD patient.[13] Before topical application of Regener-Eyes®, an MGD patient reported foreign body sensation and pain in the eyes, which were accompanied with grittiness, soreness, irritation, burning, and eye fatigue. Importantly, none of these DED-related symptoms were reported by the MGD patient after 3 weeks of Regener-Eyes® therapy.[13] Significantly improved tear film breakup time (TBUT) was noticed 3 weeks after Regener-Eyes®-based treatment, indicating restoration of meibomian gland function.[13] Complications such as ocular pain, persistent bleeding, and infections were not observed during or after the administration of Regener-Eyes®. This MGD patient did not report any adverse effects related to the Regener-Eyes®-based therapy, confirming that Regener-Eyes® is well tolerated and safe for topical application.[13]

Approximately 1 of 10 patients suffering from dry eye has underlying Sjögren's syndrome, an autoimmune disease characterized by immune cell-dependent destruction of lacrimal and salivary glands, ocular discomfort, and visual dysfunction.[21] Since Sjögren's syndrome-related dry eye is a progressive inflammatory condition, it may lead to corneal perforation, uveitis, scleritis, retinal vasculitis, and optic neuritis. Regener-Eyes® contains immunoregulatory, trophic and neuroprotective factors that could attenuate ongoing inflammation in the eye, promote epithelial cell proliferation, and prevent neural injury. Accordingly, significantly improved visual acuity, relieved ocular pain and complete healing of corneal epithelial defects were noticed in a Regener-Eyes®-treated patient with Sjögren's syndrome. Similarly, 4 weeks of Regener-Eyes®-based therapy remarkably improved visual acuity and significantly decreased ocular pain in a 26-year-old female who suffered from severe DED and epithelial basement membrane dystrophy (EBMD) with recurrent corneal erosion syndrome (RCES). Importantly, no recurrence of RCES symptoms were observed in this Regener-Eyes®-treated patient during a follow-up of 4 months, suggesting beneficial effects of Regener-Eyes® in the repair and regeneration of injured corneal epithelial cells.

Conclusions

Regener-Eyes® drops are a topical therapy for DED; they are an engineered biological product. The drops contain a large number of anti-inflammatory and trophic factors that attenuate the detrimental immune response in the eye and protect the epithelial cells of the ocular surface from injury and inflammation.[1,9,12–13,15] Topical administration of Regener-Eyes® may suppress ongoing ocular inflammation, may improve meibomian gland function, and may enhance the restoration of the ocular surface barrier in DED patients, without causing treatment-related adverse events.[1,13] Due to its potent immunosuppressive and regenerative properties, Regener-Eyes® should be considered as a powerful new therapeutic option in the management of DED.

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TESTIMONIALS

"The extraordinary efficacy of Regener-Eyes to repair the ocular surface has provided a vital tool in the management of dry eye disease. Patients see and feel the difference within a matter of a few days and it is very rewarding as an eye care professional to change the quality of vision and life in patients who have often suffered for years."

- Eric Donnenfeld, MD, FACS
(Key Opinion Leader)

"Regener-Eyes has become an essential drop in the management of my dry eye disease patients. Its unique components & effectiveness allows it to work when no other option is achieving the desired results. I've seen dramatic improvement in corneal & conjunctival staining, KCS, Sjogren's Syndrome DED & even evaporative DED cases. It can sometimes replace other inflammatory agents or be additive in improving the results. It is effective when steroids aren't an option such as steroid responders & is safe enough for long term therapy. The improvement in my patient's symptoms & signs has been impressive."

- Paul M. Karpecki, OD, FAAO
(Key Opinion Leader)

"I sincerely know Regener-Eyes gave my eyes much relief and gave me a life again, other than just caring for my eyes. Thank you for making this product that has helped me so much."

- *Regener-Eyes Professional Strength Patient*

"Results are nothing short of a miracle!"

- *Regener-Eyes Professional Strength Patient*

"After 5 months, my eyes feel almost healed from aqueous-deficient dry eye caused by chemical fume exposure. I went from thinking I was permanently disabled and in chronic pain, for over a year, to feeling 99% healed. What a journey!"

- *Regener-Eyes Professional Strength Patient*

"About one month into using Regener-Eyes Lite, I started to forget that I even had dry eyes."

- *Regener-Eyes Lite Strength Patient*

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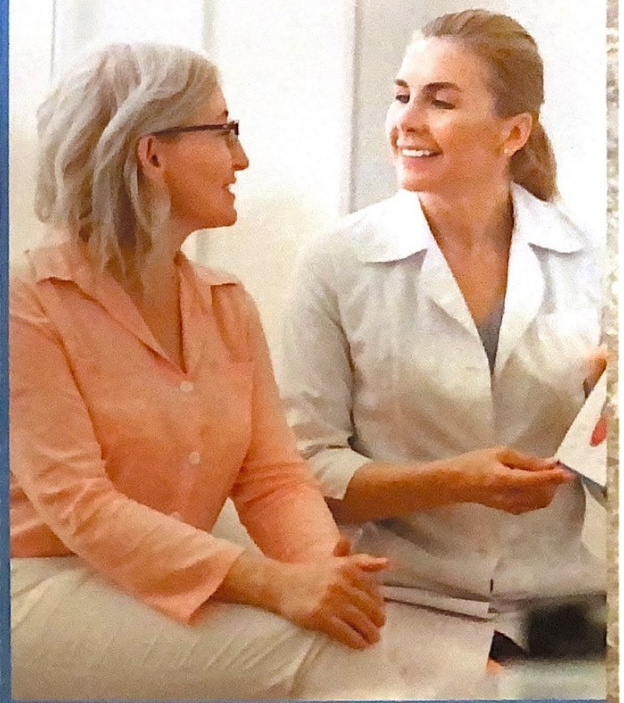

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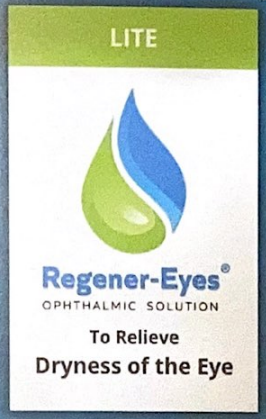
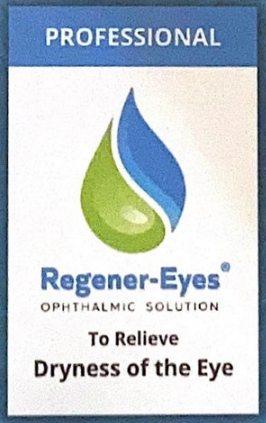


Non-Refrigerated and Formulated for Mild to Moderate Symptoms

Regener-Eyes®



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Regener-Eyes is used as a lubricant to prevent further irritation & to Relieve Dryness of the Eye.

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