Pharmaceutical Update 2023

Greg Caldwell, OD, FAAO
PSS Eyecare – Niagara Falls
Saturday, April 1, 2023

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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru, Santen
  - Disclosure: Receive speaker honorariums
- Advisory Board: Allergan, Sun, Alcon, Maculogix, Dompe, Visus, Eyenovia
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
- Optometric Education Consultants – Pittsburgh, PA, Sarasota, FL, Scottsdale/Phoenix, AZ, Orlando, FL, Mackinac Island, MI, Nashville, TN, and Quebec City, Canada - Owner

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Pharmaceutical Resource Matrix

- Commercial/Sales
  - Representatives
    - On label, educational lunches, samples, discount cards, coupons
    - Organizes the promotional dinners
- Medical Affairs- Medical Science Liaison (MSL)
  - OD, MD, PharmD, PhD,…
  - Education, education, education
  - On label or that "off label" question
  - Where the granular discussion occurs
  - No sales
- Clinical Research
  - Company sponsored studies
- Marketing
  - Assists representative on therapeutic usage
  - Consultant, advisory board, promotional speaker
- Market Access
  - Formulary access
    - Commercial and Federal payers

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MOA versus MOD

- Mechanism of Action - MOA
- Mechanism of Delivery – MOD

Mechanism of Action (Delivery) – AMPPLIFY Technology
- Mucus is a barrier for topical ophthalmic drug delivery
- AMPPLIFY utilizes two proprietary attributes
  - Nanoparticles to allow penetration into mucus pores
    - Particles smaller than 500 nm
  - Mucus penetrating surface coating
    - Prevents adherence to mucus


eyenovia

Eyenovia Announces Positive Study Results Demonstrating that its Optejet® Delivery Technology Reduces Conjunctival Cell Toxicity from Preserved Ophthalmic Solutions to a Level Comparable with Non-Preserved Solutions

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Question

Regarding the various loteprednol etabonate ophthalmic drops?

A. We have enough formulations
B. They are all the same to me
C. Help me with the differences
D. Steroids are steroids they all do the same thing
E. I will place my comment in the chat box

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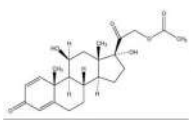
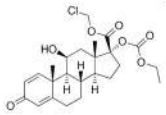


Steroids
Ketones versus Esters



- Prednisolone acetate molecule modified to undergo predictable degradation to inactive metabolites by local esterases
- Corticosteroids, C-20 ketone replaced with a C-20 ester
- C-20 ester steroids are associated with a lower incidence of IOP elevations vs. C-20 ketone steroids
  - IOP and cataracts
- Retrometabolic drug design of loteprednol aims to improve safety while maintaining efficacy

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Loteprednol Etabonate Products Ester Steroids

- Lotemax suspension 0.5%
- Alrex suspension 0.2%
- Lotemax gel 0.5%
- Lotemax SM gel 0.38%
- Inveltys suspension 1.0%
- Eysuvis suspension 0.25%
  - KPI-121

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Lotemax SM (loteprednol etabonate) 0.38%

- Indicated for the treatment of post-operative inflammation and pain following ocular surgery
- SubMicron - *Particle size* reduced to facilitate ocular penetration
  - Allowing for a decrease in drug concentration and dosing frequency (TID)
  - Increase intraocular penetration
  - Median particle diameter size reduced 5 to 12.5-fold:
    - LE gel 0.38% = 0.4-0.6 μm
    - Lotemax gel 0.5% = 3-5 μm
  - Potential for a ~10-fold increase in rate of drug dissolution
    - Based on a 10-fold increase in relative surface area with smaller particles

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Lotemax SM (loteprednol etabonate) 0.38%

- Increased concentrations demonstrated in ocular tissues
  - Cornea and aqueous humor
  - Following single topical ocular instillation of Lotemax SM 0.38% vs Lotemax gel 0.5% in rabbits
- Compared to Lotemax Gel 0.5%
  - Single topical instillation of Lotemax SM 0.38% were greater in the aqueous humor and cornea
  - Concentrations in the conjunctiva remain the highest out of the ocular tissues, with ample drug to mediate anti-inflammatory effects at the ocular surface
- Formulation advancement while maintaining a low BAK
  - Lowest concentration of BAK, 0.003% among the commercially available corticosteroid ocular drops
    - Inveltys is 0.01%

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Lotemax SM (loteprednol etabonate) 0.38%

- **Submicron formulation is designed to reduce the Lotemax Gel drug concentration 0.38% vs. 0.5%)**
- **Dosing frequency TID vs. QID**
- **Formulation builds on the heritage and advantages of Lotemax gel 0.5%:**
- **Retrometabolically designed corticosteroid**
  - Retains potent anti-inflammatory activity
  - Minimal potential for class Aes
- **Mucoadhesive, non-settling, shear-thinning gel**
  - A gel in the bottle; transitions to a liquid upon instillation
  - Becomes mucoadhesive liquid on dilution with tears
  - No need to shake - uniform dosing
  - Non-blurring

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Inveltys ™ - loteprednol etabonate suspension 1.0%

- Kala Pharmaceuticals
- August 2018
- Now in distribution centers and pharmacies
- Nanoparticle-based Mucus Penetrating Particles (MPP)
  - "Amplified Technology"
  - MOD
  - Allows drug to penetrate through tear mucins
    - Increased penetration into tissues, 3-fold to other loteprednol
- 1.0% post-operative inflammation and pain after ocular surgery
  - Dosage BID
    - First ocular corticosteroid to be BID

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Eysuvis - loteprednol etabonate suspension 0.25%

- Kala Pharmaceuticals – KPI-121
  - Approved October 27, 2020
- First prescription therapy – Specifically for the Short-Term treatment of Dry Eye Disease
  - Short term = "up to two weeks"
  - Dry eye flares – dry eye disease characterized by acute exacerbations "flares"
- Contraindications, warnings, and precautions
  - Nothing new to report
  - Delayed healing, IOP, cataracts, infections
- Adverse Reactions
  - The most common was instillation site pain, 5.0% of patients
- Safety and Efficacy based on largest clinical program in DED (n=2871)
  - Stride 1, 2, and 3 studies

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Eysuvis - loteprednol etabonate suspension 0.25%

- Dry Eye Flare – characteristics
  - Rapid onset – inflammation driven
  - Response to variety of triggers
  - Not adequately managed with patient's ongoing therapy
  - With or without maintenance therapy
    - DED patients experience flares
      - Desire rapid relief
  - Multiple episodes per year
    - 4-6 times
  - Triggers: seasonal allegies, A/C use, digital screen time, air travel, CL wearing, smoking, diet, medications
- Many chronic inflammatory and autoimmune diseases have episodic exacerbations "flares"
  - Asthma, uveitis, Sjogren's syndrome, rheumatoid arthritis, lupus erythematosus

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Eysuvis - loteprednol etabonate suspension 0.25%

- Thoughts on Dry Eye Disease
  - 80% of patients with dry eye disease suffer from flares
    - Patients may not share this at their visit
  - 45% of dry eye patients just have flares instead of continuous symptoms
  - 81% of patients using artificial tears reported flares
  - 17.2 million US patients diagnosed with dry eye disease
    - 75% never tried a prescription therapy
    - 2.9% used steroids for DED
    - 80% patients discontinue their chronic Rx medications by 4 months

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Eysuvis - loteprednol etabonate suspension 0.25%

- Mechanism of Action – AMPPLIFY Technology
  - Mucus is a barrier for topical ophthalmic drug delivery
  - AMPPLIFY utilizes two proprietary attributes
    - Nanoparticles to allow penetration into mucus pores
      - Particles smaller than 500 nm
    - Mucus penetrating surface coating
      - Prevents adherence to mucus
  - Allows rapid and enhanced ocular
    - Distribution
    - Penetration

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Tyrvaya – varenicline solution 0.03 mg

- October 21, 2021
- Nasal spray
- BID – approximately every 12 hours
- Preservative-free
- 1/33 of dosage of Chantix
  - Depression
  - Smoking cessation

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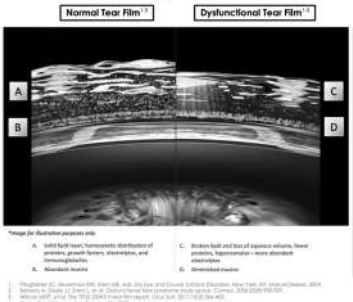
Normal and Dysfunctional Tear Film*



Natural tears contain a complex mixture of lipids, proteins, mucins and electrolytes.[3]

- Over 1,500 proteins
  - Epidermal growth factors
  - Nerve growth factors
  - Transforming growth factor beta (TGF-β)
  - Lysozymes
- 5+ lipid classes
- 20+ mucin classes

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There Is No Substitute for Natural Tear Film

Growth factors, such as nerve growth factor (NGF) and epidermal growth factor (EGF), found in natural human tears, are critical regulators for corneal wound healing.

A healthy tear film lubricates and protects the eyes from injury and infection, washes away foreign particles, and contributes refractive power for clear vision.

TFOS DEWS II tear film report

Natural tears contain a complex mixture of lipids, proteins, mucins, and electrolytes[1,2]

- Over 1,500 proteins
- 5+ lipid classes
- 20+ mucins
- Contains growth factors and has anti-inflammatory and antimicrobial properties

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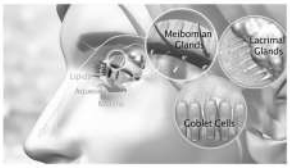
Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve is **accessible within the nasal cavity** and is activated by by OC-01 (varenicline solution) nasal spray by activation of **cholinergic receptors**.

The trigeminal nerve provides the pathway for **parasympathetic stimulation** of the lacrimal functional unit (LFU) to activate **complete basal tear film**.



34% of basal tear production is due to inhaling air through the nose[1]

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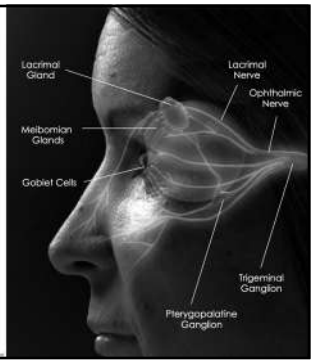
Lacrimal Gland Postganglionic Innervation[1]

- The LFU is innervated by the trigeminal nerve
- Loss of parasympathetic stimuli results in chronic reduction of tear secretion and morphologic destruction of the lacrimal gland



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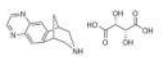
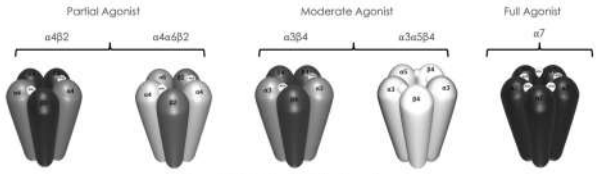
Varenicline Tartrate



- Binds with high affinity and selectivity at α-subunit containing cholinergic receptors located on the trigeminal nerve within the nasal cavity
- Water soluble and diffuses across nasal mucosa quickly



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OC-01 VNS Highlights[1-4]

- Approved as **TYRVAYA**™ (varenicline solution) 0.03 mg October 15, 2021
- Cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.
- Preservative-free, delivered as a 0.05 mL spray
  - One spray, each nostril, twice daily (approximately 12 hours apart)
  - 0.03 mg concentration | 29 mcg/spray
    0.06 mg concentration | 59 mcg/spray
- Onset of action and sustained outcomes demonstrated in clinical trials, sign outcomes measured at 5 minutes after nasal spray administration
- OC-01 VNS studied in subjects with mild, moderate, and severe dry eye disease as determined by baseline eye dryness score (EDS)
- Most common adverse reaction in clinical trials was sneezing; other adverse reactions reported in >5% of patients include cough, throat irritation, and instillation-site (nose) irritation
- 0.34 ng/mL C_{max} at 2 hours

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ACUVUE® Theravision® with Ketotifen

- First and only medication-releasing contact lens for patients who need vision correction and itchy eye relief
- Built-in allergy medication that starts to relieve itchy eyes in minutes
- Providing fast-acting and long-lasting relief
  - Up to 12 hours[5]
- Etafilcon A
- Ketotifen –antihistamine (Zaditor and Alaway)
  - Blocks histamine receptors
  - Stabilizes mast cells
  - Inhibits inflammatory cell accumulation within the eye
- Parameters
  - 8.5 mm base curve/14.2 mm diameter
  - Power Ranges
    - –0.50D to –6.00D (0.25D steps)
    - –6.50D to –12.00D (0.50D steps)

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Glaucoma

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Question

I have used netarsudil (Rhopressa or Rocklatan) in my treatment of glaucoma:

A. Yes
B. No
C. I don't treat glaucoma
D. I will place my comment in the chat box

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Rhopressa™ 0.02% (netarsudil ophthalmic solution)

- Aerie Pharmaceuticals
  - Approved December 2017
  - Treatment of glaucoma or ocular hypertension
  - Rho kinase inhibitor
    - **ROCK-NET Inhibitor**
  - Once daily in the evening
    - Twice a day dosing is not well tolerated and is not recommended
  - Side Effects
    - Conjunctival hyperemia
    - Corneal verticillata
    - Conjunctival hemorrhage

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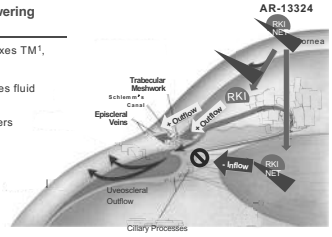
Rhopressa (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

- ROCK inhibition relaxes TM[1], increases outflow[1,2]
- NET inhibition reduces fluid production[2]
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



1. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015. 24(1):51-4.
3. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. *ARVO* 2014. Abstract 2900

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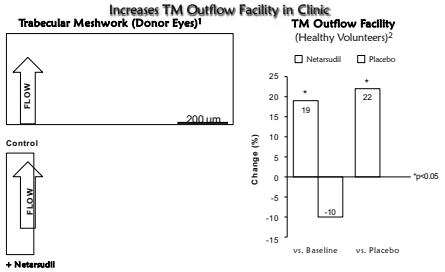
Rhopressa™ 0.02% (netarsudil)

Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic



TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein
1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at *AGS* 2017.

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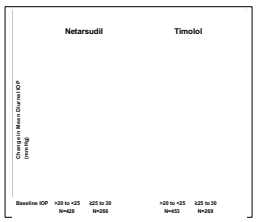
Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)



Baseline IOP >20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

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Rhopressa™ 0.02%

- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
  - Blood Pressure
    - Changes were generally small and not clinically relevant in both groups
  - Heart Rate
    - Timolol caused statistically significant reduction in the phase 3 studies by an average of 2-3 beats per month

1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 2. Kiuru et al. Association for Research in Vision and Ophthalmology oral presentation 2017 (Abstract 2461).

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Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe

Self-resolving with continued dosing

Conjunctival hemorrhage

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS301, -CS302

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Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)

Cornea verticillata

AR-13324-CS302 netarsudil QD subject

AR-13324-CS302 netarsudil BID subject

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS302

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Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*

Phospholipids accumulation

Control | Amiodarone | Netarsudil

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IFH07
* Rajman MB et al. Surv. Ophthalmol. 2017;62:286-301

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My Experience

OD treated OS gtts

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Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia
- 54.4% TEAE
- Severity did not increased with continued dosing
- Sporadic

Cornea Verticillata
- 20.9% TEAE
- Asymptomatic
- 7.4% experienced reduced visual acuity
- Not clear to a directly associated
- All resolved after 13 weeks of D/C

Conjunctival Hemorrhage
- 17.2% TEAE
- Mild in severity and transient
- Self-resolving with continued dosing

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Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition

- Thank you, Charles McBride, O.D., Beaverton, OR (12-23-2020 OGS – Google Groups)
- Sample of Rocklatan yesterday to lower his IOP of 46mmHg
- IOP today was 34
- Didn't measure corneal thickness
- The eye is blind and pretty sure it is neovascular glaucoma
- He's not been seen in three years and recently relocated from Missouri

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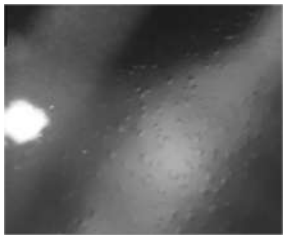
Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition Graft Patient



Thank you! Joe Shovlin, OD, FAAO

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Rocklatan™

(netarsudil/latanoprost ophthalmic solution)
0.02%/0.005%

- Aerie pharmaceuticals
  - March 14, 2019
- Once-daily eye drop
- First PGA combination approved
  - Superiority versus inferiority
- Refrigeration
  - Storage and after opening
    - For now

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Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%

- Bausch & Lomb
  - previously Vesneo™
- November 2, 2017; approved
- Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
- Once daily monotherapy
- Dual mechanism of action
  - Uveoscleral pathway to increase aqueous humor outflow
  - Butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
- Ocular adverse events
  - Conjunctival hyperemia, eye irritation, eye pain and instillation site pain
  - Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur

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Durysta™ (Bimatoprost Implant)

- Allergan
  - Approved May 23, 2020
- Indication: Intracameral administration for the reduction of intraocular pressure in patients with Open Angle Glaucoma or Ocular Hypertension
- Sustained-Release, biodegradable intracameral implant
- Intracameral implant containing 10 mcg in the drug delivery system
- Contraindications:
  - Active or suspected ocular or periocular infections
  - Corneal endothelial cell dystrophy (e.g. Fuch's Dystrophy)
  - Prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK])
  - Absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment
  - Hypersensitivity to bimatoprost or any other components of the product

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Durysta™ (Bimatoprost Implant)

- Warnings and Precautions
  - Corneal adverse reactions
    - Bimatoprost implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss
  - Iridocorneal angle:
    - Bimatoprost implant should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3)
    - Anatomical obstruction (e.g. scarring) that may prohibit settling in the inferior angle
  - Macular edema
    - Bimatoprost implant should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
  - Intraocular inflammation
  - Pigmentation
  - Endophthalmitis

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Durysta™ (Bimatoprost Implant)

- Dosage and Administration
  - Bimatoprost implant is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant
  - Should not be readministered to an eye that received a prior bimatoprost implant
    - On label
- Efficacy
  - Demonstrated in two Phase 3 studies
  - IOP reduction of approximately 5 - 8 mmHg
  - In patients with a mean baseline IOP of 24.5 mmHg

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Question

Did Combigan go generic?

A. Yes
B. No
C. I don't treat glaucoma
D. I will place my comment in the chat box

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April 19, 2022

Screenshot from Pharmacompass

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Pictures Taken February 21, 2022

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2-2-2022

Screenshot from Carlisle Medical

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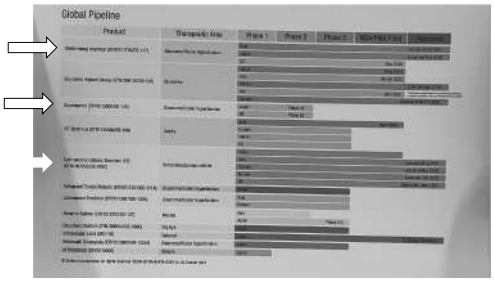
What is Coming?



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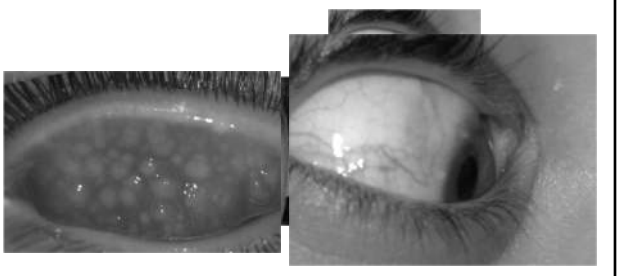

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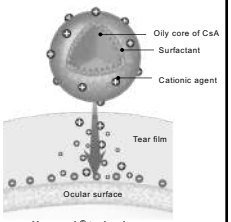
Verkazia – cyclosporine ophthalmic emulsion 0.1%

- Approved June 2021 – Santen
- Coming March/April 2022
- Treatment of Vernal Keratoconjunctivitis (VKC)
- NOVASORB® Technology
- Novasorb® is a positively charged nanoemulsion containing droplets of CsA in an aqueous phase. Each droplet has an oily core which solubilizes the CsA and a coating of surfactants to stabilize the emulsion2
- The positively charged droplets are attracted to the negatively charged cell membranes of the ocular surface structures, which helps Verkazia to spread, increase ocular residence time, and improves its absorption1-3



Novasorb® technology

1. Daull P, et al. *J Pharm Pharmacol*. 2014;66:531-541. 2. Lallemand F, et al. *Mucosal Delivery of Biopharmaceuticals*. New York: Springer Science Business Media; 2013.
3. Lallemand F, et al. *J Drug Deliv*. 2012;2012:804284. 4. Baudouin C, et al. *Eur Ophthal Rev*. 2015;9:121-127.

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Verkazia – cyclosporine ophthalmic emulsion 0.1%

- Indication: For the treatment of VKC in children and adults
- Dosage and administration
  - One drop administered four times daily (morning, noon, afternoon, and evening) into each affected eye
  - Drops should be milky white
  - Immediately after use, discard the remaining contents from the single-dose vials
  - Treatment can be discontinued after signs and symptoms are resolved and can be reinitiated if there is a recurrence

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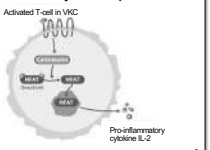
Verkazia® Proposed Mechanism of Action

Verkazia® contains cyclosporine, an immunomodulatory agent that disrupts inflammation and allergic responses[1]

Calcineurin stimulates the pro-inflammatory T-cell response



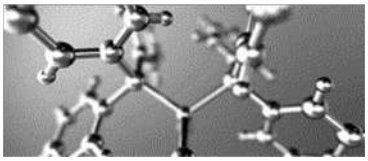
Additional anti-inflammatory effects of cyclosporine include[2]:
- Inhibition of histamine release from mast cells
- Interfering in the allergy process
- Increased expression of anti-inflammatory cytokines

Cyclosporine inhibits calcineurin and blocks pro-inflammatory cytokines

Cyclosporine is bound by the cyclophilin family of proteins within T-cells. IL, interleukin; NFAT, nuclear factor of activated T-cells.
1. Verkazia® (cyclosporine ophthalmic emulsion) 0.1%, for topical ophthalmic use [package insert]. Emeryville, CA: Santen Inc; 2021. 2. Leonardi A. Ophthalmol Ther. 2013;2:73-88.

54

Adrenergic Alpha Receptor Agonists



55

Adrenergic Alpha Receptor Agonists

- Iopidine 0.5%, 1.0%
  - Apraclonidine
- Alphagan and Alphagan P - 0.2%, 0.15%, and 0.10%
  - Brimonidine tartrate
  - IOP lowering and miosis
- Lumify 0.025%
  - brimonidine tartrate
  - Redness reducer, no pupil response
- Naphcon-A 0.025%
  - Naphazoline hydrochloride 0.025%
  - Acting on alpha-adrenergic receptors in the arterioles of the conjunctiva
- Visine 0.05%
  - Tetrahydrozoline HCl
- Upneeq 0.1%
  - Oxymetazoline hydrochloride
- Oxymetazoline hydrochloride
  - OTC nasal spray
    - 0.05% solution
- OTC eye drops
  - 0.025% solution
- RX topical cream
  - 1% cream
  - Rosacea

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Question

I have used Upneeq (oxymetazoline HCl) ophthalmic solution 0.1% on my patients:

A. Yes
B. No
C. I will place my comment in the chat box

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UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Osmotica Pharmaceuticals
  - RVL, Trigen, and Veritical
  - Approved July 9, 2020
- Indicated for the treatment of acquired blepharoptosis in adults
  - Non-surgical treatment for acquired blepharoptosis
- Preservative-free balanced salt solution containing hypromellose
- Warning and Precautions
  - Alpha-adrenergic agonists as a class may impact blood pressure
  - Advise UPNEEQ patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens
  - Use UPNEEQ with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome
  - UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma

58

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Adverse reactions
  - 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache
- Drug interactions
  - Alpha-adrenergic agonists, as a class, may impact blood pressure.
  - Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised
  - Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy

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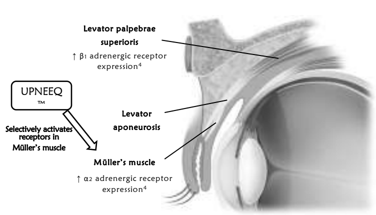
Mechanism of Action

- **Oxymetazoline** is a potent, direct-acting α-adrenergic receptor agonist with a **~5:1 affinity for α2:α1 receptors**[1,2,3]
- When applied to the eye, UPNEEQ is thought to stimulate **contraction of Müller's muscle**, raising the upper eyelid



References: 1. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. *Fundam Clin Pharmacol.* 2010;24(6):729-739. **2.** Sugden D, Anwar N, Klein D. Rat pineal α1-adrenoceptor subtypes: studies using radioligand binding and reverse transcription-polymerase chain reaction analysis. *Br J Pharmacol.* 1996;118(5):1246-1252. **3.** Hosten LO, Snyder C. Over-the-counter ocular decongestants in the United States – mechanisms of action and clinical utility for management of ocular redness. Clin Optom. 2020;12:95-105. **4.** Esmaeli-Gutstein B, Hewlett B, Pashby R, Oestreicher J, Harvey J. Distribution of adrenergic receptor subtypes in the retractor muscles of the upper eyelid. *Ophthalmic Plast Reconstr Surg.* 1999;15(2):92–99.
60

60

UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

- Dosing: One drop administered topically to ptotic eye(s), once per day
- Met both primary and secondary efficacy endpoints in phase 3 studies
  - Once-daily resulted in significant improvement
    - Upper visual field
    - Upper eyelid elevation (MRD-1)
  - Upper eyelid elevation was rapid and sustained
    - Significant improvement evident within 5 minutes of instillation in one study
    - Peak effect – 1 hour
    - Lasts – 8 hours

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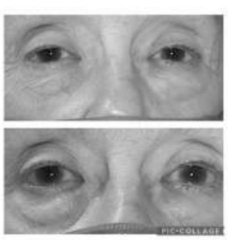
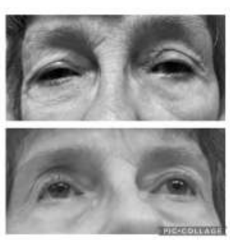
UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%





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UPNEEQ™ - Oxymetazoline HCl ophthalmic solution 0.1%

63

Vuity – Pilocarpine 1.25%

- Approved October 29, 2021
- Indication: Cholinergic muscarinic receptor agonist indicated for the treatment of presbyopia in adults
- Dosage: QD
- Warnings: Poor illumination and iritis, RD?
- Significant amount of Rx's written since launched
  - Optometry is leading the charge in writing for Vuity
- $79 is the cost at most pharmacies
- My Vuity Points
  - Buy 4 the 5th is free
- UpScript
  - Online pharmacy
  - Direct ship to the patient
- Re-engineered design of pilocarpine, optimized concentration, pHast technology
- Efficacy – 3 line gain, significant improvement for intermediate/device vision
- Safe: 1.3% discontinuation rate due to adverse effects

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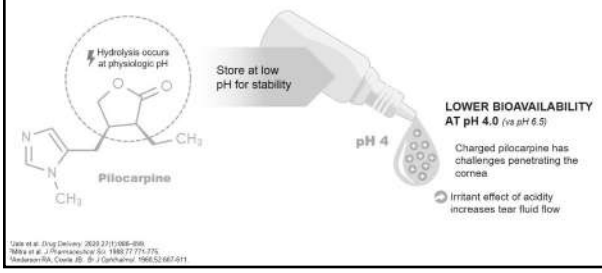
All Pilocarpine formulations are stored at low pH to maintain stability[1-3]



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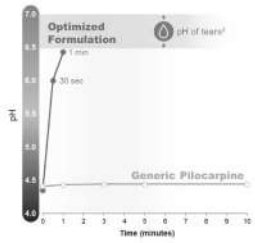
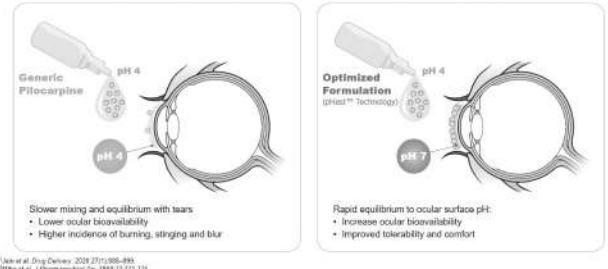
Optimized Formulation Rapidly Adjusts to Neutral pH After Administration



- The **Optimized Formulation with pHast™ Technology** equilibrated to physiologic pH within 1 minute[1]
- In vitro studies showed that the pH of **Generic Pilocarpine** did not reach physiologic pH in simulated tear fluid, even after 10 minutes[1]

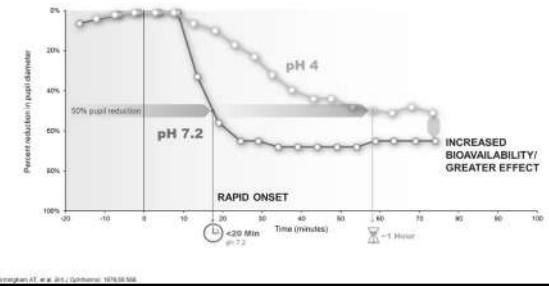
66

Optimized Formulation Improves Bioavailability and Tolerability[1-4]



67

The pH of Pilocarpine Affects Its Onset of Action and Bioavailability[1]



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What's Coming Soon?

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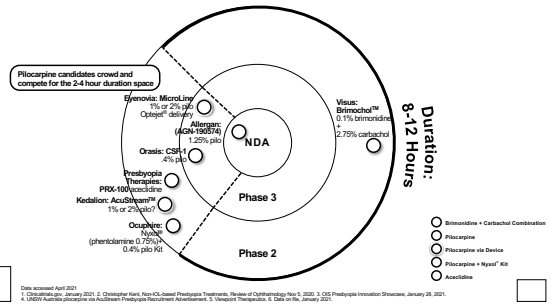
Pharmacologic Treatments for Presbyopia Are Coming, With Miotic Drops Occupying the Majority of Development

Topical Drops in Development	Active Ingredient(s)	Mechanism of Action
Brimochol™ (Visus Therapeutics)	Carbachol + brimonidine tartrate	Carbachol: Miotic Brimonidine tartrate: Prevents pupil dilation, inhibits contraction of ciliary muscle, increases bioavailability of carbachol[1,2], prevents redness[3]
CSF-1 (Orasis)	Pilocarpine	Miotic
PRX-100/Liquid Vision (Presbyopia Therapies)	Acecildine	Miotic
AGN 190584 (Allergan)	Pilocarpine	Miotic
MicroLine/OpteJet (Eyenovia)	Pilocarpine	Miotic
AcuStream™ (Kedalion)	Pilocarpine	Miotic
Nyxol® and Pilocarpine Combination Kit (Ocuphire)	Phentolamine mesylate and pilocarpine	Miotic (both pilocarpine and phentolamine mesylate products) Vasodilates small muscles (phentolamine mesylate product)[4]
True Vision Treatment® Contact lenses and Eye Drops Kit (Yolia Health)	Hyaluronidase and collagenase	Alters cornea[7]
UNR844 (Novartis)	Lipoic acid choline ester	Lens-softening agent
VP1-001 (Viewpoint Therapeutics)	Stabilizing alpha-crystallin molecule	Target's protein misfolding to restore native, functional shape[8]

1. Suzuki et al. Ocular and Systemic Pharmacokinetics of Brimonidine and Timolol After Topical Administration in Rabbits: Comparison Between Fixed-Combination and Single Drugs. *Ophthalmol Ther* (2020) 9:115–125. 2. Allergan patent application (Pub. No.: US 2018 / 0370035 A1). 3. LUMIFY® Product Insert www.fda.gov accessed 9/24/2020. 4. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition), 2009. 5. Korczyn et al. Effect of Pilocarpine on Intraocular Pressure in Normal Humans. Ophthalmic Res. 14:182-187 (1982). 6. Pepose. Phentolamine Mesylate Ophthalmic Solution Provides Long Lasting Pupil Modulation and Improves Visual Acuity. ARVO 2020 Abstract: #3264450. 7. Yolia Health. 8. Viewpoint Therapeutics, February 2021.

70

U.S. Presbyopia Miotic Drop Landscape is Crowded in the Short-acting Space



Data accessed April 2021
1. Clinicaltrials.gov, January 2021. 2. Christopher Kent, Non-IOL-based Presbyopia Treatments, Review of Ophthalmology Nov 5, 2020. 3. OIS Presbyopia Innovation Showcase, January 28, 2021. 4. UNDAY Australia pilocarpine via AcuStream Presbyopia Recruitment Advertisement. 5. Viewpoint Therapeutics. 6. Data on file, January 2021.

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March 16, 2022

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March 16, 2022

Press Release: Visus Announces Appointment of Julia Williams as VP of Clinical and Medical Affairs and Expansion of Irvine Co-Headquarters

- March 22, 2022- Visus announced the launch of our two pivotal Phase 3 trials
  - (BRIO-I and BRIO-II) for BRIMOCHOL™ PF.
- BRIO-I and BRIO-II are double-masked, randomized, multi-center, safety and efficacy studies expected to enroll emmetropic phakic and pseudophakic presbyopic patients
  - Approximately 170 and 500 respectively

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Two Categories of Presbyopia Drops

- **Miotic drops** increase depth of field by inducing a pinhole effect
  - Low risk, highly effective and easily reversible compared to surgical alternatives
  - Miotic drops aren't without side effects – headache, brow ache, IOP fluctuations, myopic shift and hyperemia[1,2]
- **Lens softening topical agents** intend to increase ability to accommodate with usage over time

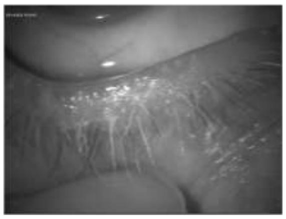
1. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas (Eighth Edition), 2009. 2. Korczyn et al. Effect of Pilocarpine on Intraocular Pressure in Normal Humans. *Ophthalmic Res.* 14:182-187 (1982).

74

Demodex Blepharitis and a New Therapeutic on the Horizon

75

What's the Diagnosis?



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Demodex Infestation

- Collarettes are pathognomonic sign of Demodex Infestation
- Collarettes are composed of mite waste products and eggs
  - Regurgitated undigested material combined with epithelial cells, keratin, and mite eggs

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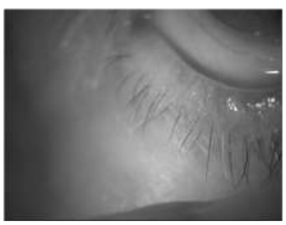
Demodex Before and After



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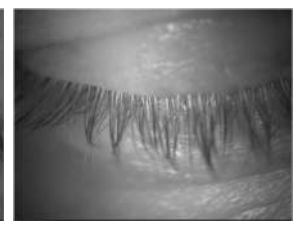
Demodex Before and After



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DEMODEX BLEPHARITIS | A PERVASIVE AND DAMAGING EYE DISEASE

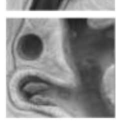
- **Blepharitis is the inflammation of the eyelids** causing irritation and redness
- **69% of blepharitis cases are due to *Demodex* infestation leading to *Demodex* blepharitis[1-4]**
  - *Demodex* mites are implicated in other diseases of the lid and lid margin, including blepharitis and meibomian gland dysfunction[2,3]
  - *Demodex* mites are associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, perioral and scalp hair loss, and basal cell carcinoma[1,3]
- ***Demodex folliculorum* and *Demodex brevis*** are the only 2 species found in humans[5]
  - The life cycle of the *Demodex* mite is approximately 14 to 18 days from the egg to the larval stage followed by the adult stage[5]
  - The life span of the mite is limited outside the living body; direct contact is required for transinfestation[5]

D. folliculorum

0.3-0.4 mm length
Colonizes the base of the lash follicle[2]

D. brevis

0.1 mm length
Colonizes the meibomian gland[2]



1. Mayo Clinic. Accessed June 28, 2022. https://www.mayoclinic.org/diseases-conditions/blepharitis/symptoms-causes/syc-20370141 **2.** Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. **3.** Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. **4.** Trattler W et al. *Clin Ophthalmol*. 2022;16:1153-1164. **5.** Litwin D et al. *Iran J Parasitol*. 2017;12(1):12-21.

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DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

Image courtesy of Laura M. Periman, MD, used with permission.[1]

MECHANICAL

- Lash distension occurs as *Demodex* mites attach to follicles[2-4]
- *Demodex* mites deposit debris and digestive enzymes, causing further irritation to the eyelid margin[4,5]

BACTERIAL

- *Demodex* mites can contribute to blepharitis by carrying bacteria on their exterior surface that may elicit immune responses[3,6-7]

CHEMICAL

- *Demodex* mites have been associated with altered meibum composition[8]
- Debris from *Demodex* mites can potentially lead to chronic inflammation and degeneration of conjunctival tissue[9]

1. Data on file. Images courtesy of Laura M. Periman, MD; 2022. **2.** Zhang AC et al. *Ophthalmic Physiol Opt*. 2020;40(4):389-432. **3.** Liu J et al. *Curr Opin Allergy Clin Immunol*. 2010;10(5):505-510. **4.** Fromstein SR et al. *Clin Optom (Auckl)*. 2018;10:57-63. **5.** Gao YY et al. *Invest Ophthalmol Vis Sci*. 2005;46(9):3089-3094. **6.** Zhu M et al. *Front Microbiol*. 2018;9:1719. **7.** Li J et al. *Ophthalmology*. 2010;117(5):870-877. **8.** Gao H et al. *Transl Vis Sci Technol*. 2021;10(14):6. **9.** Tarkowski W et al. *Biomed Res Int*. 2015:259109.

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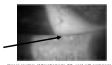
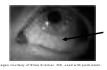
CLINICAL MANIFESTATIONS OF *DEMODEX* BLEPHARITIS

Disorders of Eyelashes[1,2]
Infestation of the lash follicles can result in collarettes and may lead to malalignment, trichiasis, and madarosis



Meibomian Gland Dysfunction[1,2]
Blockage leads to filling, swelling, and many enlarged glands (cysts) or infection. Chalazia are common granulomatous responses

Lid Margin Inflammation[1,2]
Severe lid margin inflammation can be caused by mechanical blockage and a delayed host immune hypersensitivity reaction



Conjunctival Inflammation[1,2]
Without proper hygiene, lid margin inflammation may spread over to the conjunctiva producing a condition known as blepharoconjunctivitis

Corneal Manifestations[1,2]
D. brevis is commonly associated with inflammation that spreads to the cornea, causing sight-threatening corneal lesions, superficial vascularization, marginal infiltrates, phlyctenule-like lesions, opacity, and/or nodular scars

1. Liu J et al. *Curr Opin Allergy Clin Immunol.* 2010;10(5):505-510. 2. Chang AM et al. *Curr Opin Ophthalmol.* 2015;26(4):295-300.

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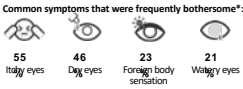
THE NEGATIVE BURDEN OF *DEMODEX* BLEPHARITIS IS VERY REAL

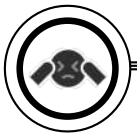
80% of patients report negative impact on daily life*

- **Atlas** multicenter, observational study (N=311)
- Evaluated the clinical and patient-reported impact of *Demodex* blepharitis
- Inclusion criteria:
  - At least 1.0 mites per lash
  - >10 collarettes on the upper eye lid
  - At least mild erythema (redness)

Common symptoms that were frequently bothersome*:



55 Itchy eyes %
46 Dry eyes %
23 Foreign body sensation %
21 Watery eyes %



51% Experienced signs and symptoms ≥4 years

58% Never diagnosed with blepharitis

33% Made at least 2, and sometimes >6, visits to a doctor for this condition

Early identification of *Demodex* blepharitis is critical due to long-term symptoms that have a significant impact on patients

*Per an observational study of adult *Demodex* blepharitis patients from 8 US ophthalmic and optometric centers. O'Dell L, Donker DL, Devries DA et al. Psychosocial impact of Demodex blepharitis. Clin Ophthalmol. 2022; 16:2999-2987.

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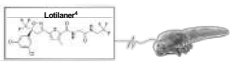
MECHANISM OF ACTION OF TP-03 (Lotilaner Ophthalmic Solution 0.25%)

TP-03 : Lotilaner ophthalmic solution 0.25%
(Tarsus Pharmaceuticals, Inc.)

- Lotilaner functions as a noncompetitive antagonist of mite and arachnid GABA-gated chloride channels[1,2]
- Directly paralyzes the mite nervous system through parasite-specific GABA inhibition, leading to death[1,2]
- The lipophilic nature of the drop suggests its ability to flow into the oily sebum of the lash follicle where the mites reside[3]

NOTE: Currently not FDA approved, in development and for investigational use only. There are currently no FDA-approved therapeutics for *Demodex* blepharitis



Product form[4]
Preserved (sorbate) multidose eye drop solution in bottle

Dosing[4]
Twice daily for 6 weeks

FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid.
1. DailyMed Credelio. Accessed June 28, 2022. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=627f2ebc-ce24-452b-bbb3-45d4e9f8e2b0 2. Gonzalez-Salinas R et al. *J Ophthalmol.* 2021:3862684. 3. Liarildo. Accessed June 28, 2022. https://www.globenewswire.com/news-release/2022/05/03/2434548/0/en/Liarildo-Partner-Tarsus-Pharmaceuticals-Announces-Positive-Topline-Data-from-Second-Pivotal-Trial-of-TP-03-for-the-Treatment-of-Demodex-Blepharitis.html
4. Chemfon Lotilaner. Accessed June 28, 2022. https://www.chemron.com/en/cas/1369852-71-0_1262257.html& 5. Hu E et al. Cornea. 2022; In Press.

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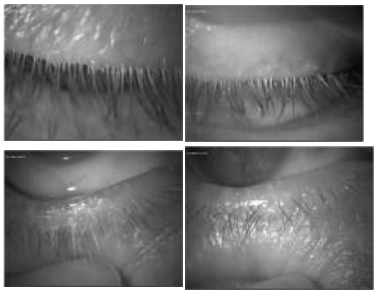
Demodex



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TP-03 by Tarsus is a Novel Drug Designed to Treat Demodex Blepharitis by Eradicating Mites and Collarettes

Product Form	Multi-dose eye drop solution bottle, preserved
Targeted Use	Treatment of Demodex blepharitis
MOA	Paralysis and death of Demodex mites
Diagnosis	Collarettes identified in standard eye examination
Dosing	BID* for 6 weeks
Efficacy Goal	1° collarette cure, 2° mite eradication, 2° redness + collarette cure
Safety Goal	Well-tolerated safety profile

* TP-03 Product profile based on Phase 2 trial design

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Ocular Biologics

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Question

Which biologic drug has been used in eye care the longest?

A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

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Treatments for Choroidal Neovascularization (CNV)

- Where is all started in the eye
- Disorders of the blood vessels in the retina are responsible for some of the most common causes of blindness in the world
  - Retinopathy of prematurity
    - Important cause of blindness in children in middle-income countries
  - Diabetic retinopathy
    - Common cause of blindness in the working-age population of industrialized countries
  - Age-related macular degeneration
    - A common cause of blindness in the world
- These conditions are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF)
- VEGF was discovered in the 1980s and is important in the growth and development of blood vessel in tumor growth
  - 1994 it was proven that retinal hypoxia produces VEGF

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Treatments for Choroidal Neovascularization (CNV)

- Current Anti-VEGF treatments
  - Pegaptanib (Macugen)
    - First FDA Approved December 2004
    - RNA aptamer
    - AMD
  - Bevacizumab (Avastin)
    - Humanized full length monoclonal antibody - 2005
    - AMD
  - Ranibizumab (Lucentis)
    - Humanized monoclonal antibody fragment – 2006
    - AMD, DME, DR, RVO
  - Aflibercept (Eylea)
    - Fusion protein – 2011
    - AMD, DME, DR
  - Brolucizumab-dbll (Beovu)
    - Humanized single-chain antibody fragment - 10-8-2019
    - Up to 3 months dosing intervals, most are 4-6 weeks
      - 50% remained 3 months after 1 year

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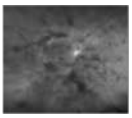
Beovu (brolucizumab)

- Indication: injection is used for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
  - **Offers a 3-month dosing schedule in the first year of treatment**
- Warning issued by the American Society of Retinal Specialists about a series of intraocular inflammation events—some of which led to severe vision loss
- On April 8, 2020, Novartis announced its completion of the review, which included an assessment by an external, independent Safety Review Committee
- Complications: n=1098
  - Intraocular inflammation (IOI) - 4.6% (n=50)
  - IOI + retinal vasculitis – 3.3% (n=36)
  - IOI + retinal vasculitis –retinal (artery) vascular occlusion – 2.1% (n=23)
  - Vision loss of 15 letters or more - <1%



91

Question

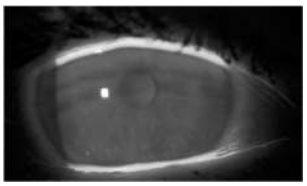
Which biologic drug is indicated for the treatment of neurotrophic keratitis?

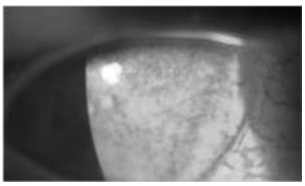
A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

92

Stain Without Pain!

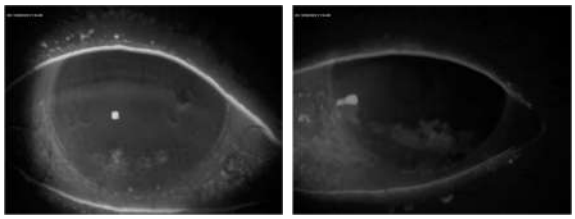
Actually, the OS is More Comfortable – What?





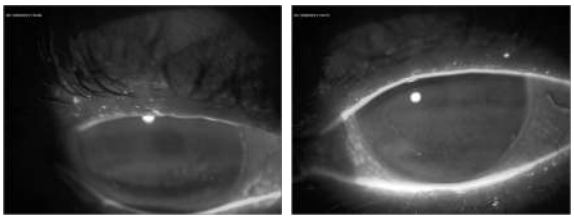
93

Before Oxervate™ (cenegermin-bkbj) Treatment



94

After Oxervate™ (cenegermin-bkbj) Treatment



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Corneal Sensitivity

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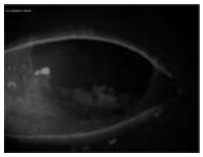
Oxervate™ (cenegermin-bkbj)

- Grading corneal sensitivity: (Cotton Tip)
  - Normal
  - Reduced
  - Absent
  - Reduced in all quadrants and centrally
  - Absent inferior quadrant, reduced everywhere else
- Neurotrophic Keratitis: (Staining)
  - Mild – Stage 1
  - Moderate – Stage 2
  - Severe – Stage 3



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Neurotrophic Keratitis is a Degenerative Disease

- The Mackie classification represents one way to assess or grade NK – stage or progression

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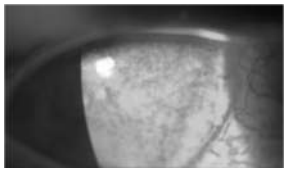
Mackie Classification

Moderate - Stage 2

Moderate - Stage 2



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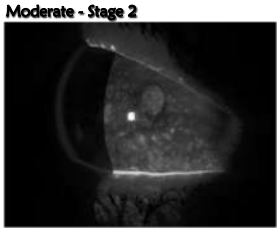
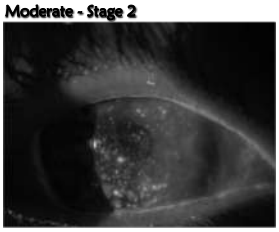
Mackie Classification

Moderate - Stage 2

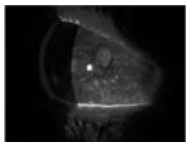


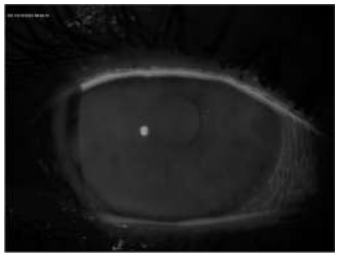
Moderate - Stage 2



100

Resolved





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Oxervate™ (cenegermin-bkbj)

- Approved 2018 (August 28, 2018)
- Dompe farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Used as eye drop
    - Not infused or injected
- Storage issues: in the freezer at the pharmacy
  - Patient keeps the individual vials in the fridge – once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
  - None

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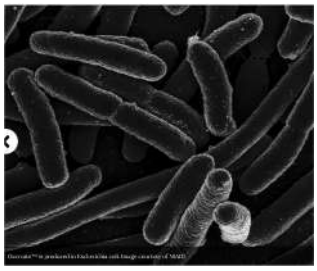
Escherichia Coli



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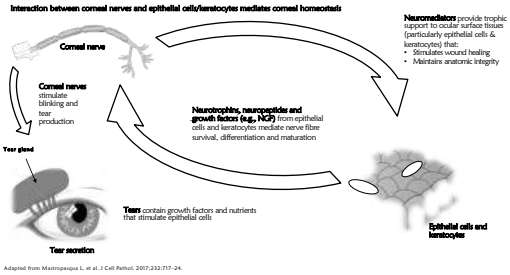
Corneal Homeostasis



Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24.

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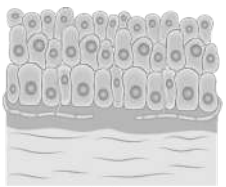
Pathophysiology of NK[1]

- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK

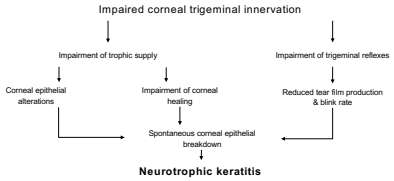


Penetration of nerves into the epithelium

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717-24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521-42.

105

Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L., et al. J Cell Pathol. 2017;232:717–24.

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Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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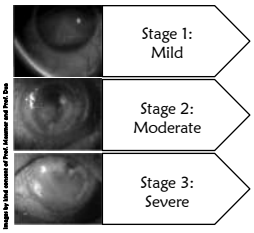
NK classification



Images by kind consent of Prof. Al-Aqaba and Prof. Dua

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semeraro F, et al. Ophthalmologica 2014;231:191-7; 2. Sacchetti M & Lambiase A. Clin Ophthal

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Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis[1]

Ocular symptoms
History
Clinical examination and tests

NK suspected

Test corneal sensitivity
- Normal → NK unlikely
- Reduced → Further tests required

Corneal sensitivity tests:[2]
- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]: 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS:[1]

CORNEAL INNERVATION
NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]

CELL PROLIFERATION AND DIFFERENTIATION
NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

TEAR SECRETION
NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5) 521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Mauli S, Colafrancesco V, Sorrelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2000;29:1163–1168

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Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s[1]
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein[2]

1. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

* *Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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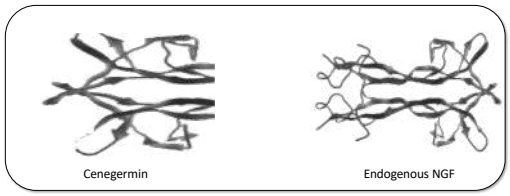
Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Dosing and Administration

Instill 1 drop of OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

2 — **Every 2 hours**

6 — **Apply 6 times daily**

8 — **Continue for 8 weeks**

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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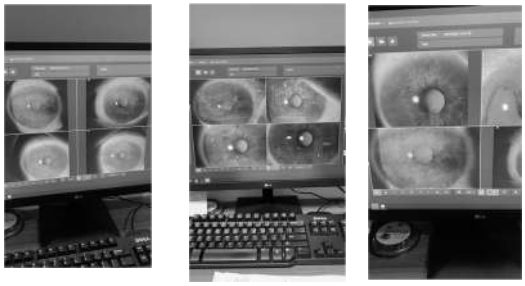
Let's Hear From a Patient

April 7, 2020 - After 1 week

April 21, 2020 - After 3 weeks

May 12, 2020 - After 6 weeks



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Study Conclusions

After 8 weeks of treatment, 6 times daily

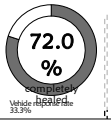
In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

50 clinical trial sites in Europe and the U.S.

Study NGF0212 (REPARO) (N=52 per group)

European patients with NK in one eye

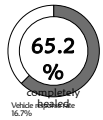
NCT01756456



Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Of patients who healed after one 8-week course of treatment… **80%** Remained healed for one year*

*Based on REPARO, the study with longer follow-up

Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[1]

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J BDC, K D et al. Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE); 10–13 June, 2017, Barcelona, Spain. 2017. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

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OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
  - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
  - Lenses may be reinserted 15 minutes after administration.

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Thyroid Disease and Thyroid Eye Disease

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Optometric Education Consultants

Question

Which biologic drug is indicated for the treatment of thyroid eye disease?

A. Oxervate™ cenegermin-bkbj
B. Tepezza™ teprotumumab-trbw
C. Actemra™ tocilizumab
D. Avastin™ bevacizumab
E. I don't know

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Tepezza?

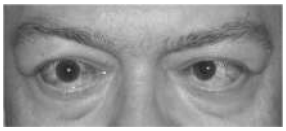

Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of ≥8° in last 1–3 months

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Questions Thank You!

Pharmaceutical Update 2023

Greg Caldwell, OD, FAAO
PSS Eyecare – Niagara Falls
Saturday, April 1, 2023

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