

Pharmaceutical Update 2024


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Disclosures- Greg Caldwell, OD, FAAO
All relevant relationships have been mitigated

- Lectured for: Alcon, B&L, BioTissue, Dompé
- Disclosure: Receive speaker honorarium
- Advisory Board: Dompé, InnovoGen, Iveric
- Disclosure: Receive participant honorarium
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
- Disclosure: Non-salaried financial affiliation with Pharmacia
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
- 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 – Scottsdale, AZ, Pittsburgh, PA, Sarasota, FL, Barcelona, Spain, Orlando, FL, Mackinac Island, MI, Quebec City, Canada, and Nashville, TN- Owner



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My Practice

I am a clinician first then a scientist

- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid, showing clinical applications of the science








It is wonderful to have someone who's juggling so many aspects of optometry (scientific, clinical experience, teacher & lecturer). It is refreshing and very informative. -Sarah

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"The Comfort Zone"



Confidence
Capable
Courage
Commitment



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Pharmaceutical Resource Matrix

- Commercial/Sales
 - Representatives
 - On food, educational lunches, samples, discount cards, coupons
 - Organize the promotional dinner
- Medical Affairs- Medical Science Liaison (MSL)
 - MD, PhD, 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
 - Anti-representative or therapeutic usage
 - Consultant, advisory board, promotional speaker
- Market Access
 - Formulary access

© Commercial and Medical Affairs

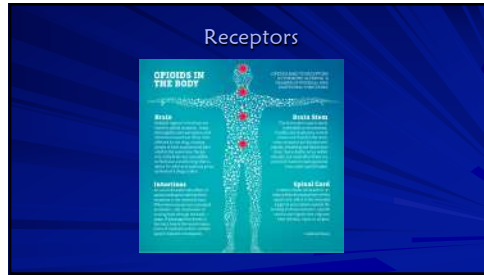
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If you have a glaucoma practice you have an ocular surface disease practice

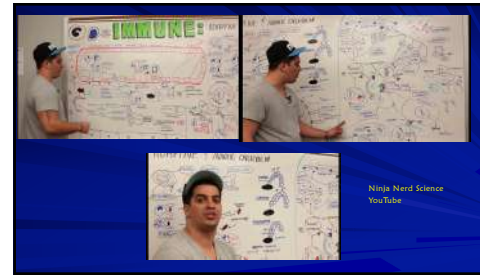



Follicular Conjunctivitis
Superficial Punctate Keratitis (SPK)

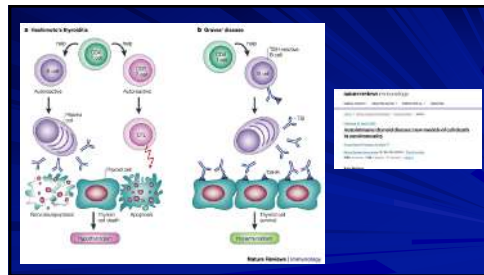
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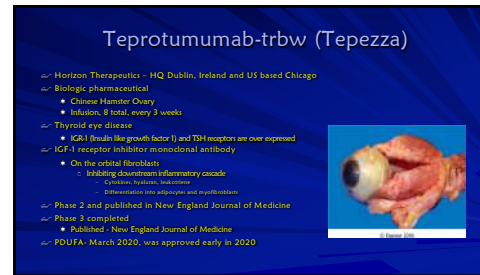
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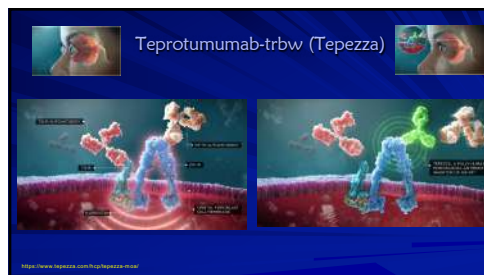
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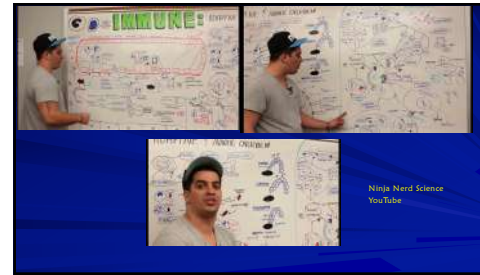
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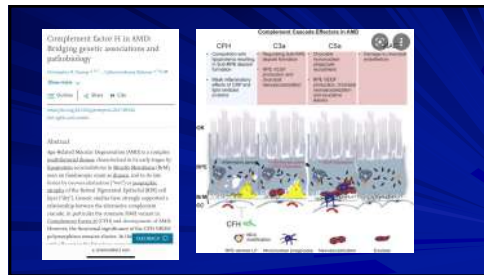
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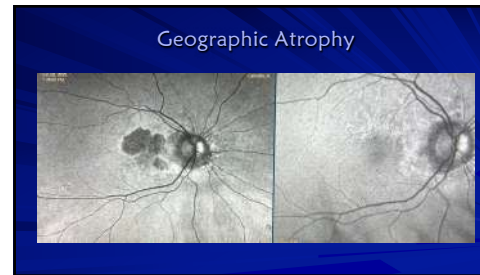
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Syfovre (pegcetacoplan injection)

- Apellis Pharmaceuticals
- February 2023 – approved
- Indications: Treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD)
- Mechanism of action: targeted C3 inhibition therapy
 - Regulating excessive activation of the complement cascade, which could lead to the onset and progression of diseases
- Administered: Intravitreal injection
- Macular degeneration is associated with overaction of the complement system
- C3 activation – inflammation, phagocytosis, cell membrane disruption
- C3 inhibitor is mechanism of action (MOA)
 - Synthetic, peptide-based inhibitor of C3
 - Prevents overactivation

The diagram illustrates the complement system, highlighting the activation of C3 and its role in inflammation and cell membrane disruption. It shows how Syfovre acts as a C3 inhibitor to prevent overactivation.

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Izervay (avacincaptad pegol intravitreal solution)

- Iveric Bio
- August 2023 – approved
- Indications: treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
- PEGylated RNA aptamer
- Mechanism of action: complement C5 inhibitor formulated to slow GA progression
- Macular degeneration is associated with overaction of the complement system

The diagram illustrates the complement system, highlighting the activation of C5 and its role in GA progression. It shows how Izervay acts as a C5 inhibitor to slow GA progression.

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Inflammatory Lifestyle, Genetics, Epigenetics, and Over Reactive Immune System

Evidence Based Medicine Evidence Informed Risk Adjusted Medicine

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Aptamer versus Antibody

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Small Molecule Drugs versus Biologics

- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
 - Organic chemistry
 - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
 - Genetic engineering – is the closest manufacturing process of a biologic drug

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Size and Complexity of Biologic Drugs

- Small molecule drugs can be taken orally
 - Tend to work in the body within cells
- Biologics are significantly larger in size
 - Typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells
- Small molecule drugs
 - Such as aspirin
 - Composed of only 20 to 100 atoms
- Small biologics
 - Such as hormones
 - Composed of 200 to 3000 atoms
- Large biologics
 - Such as antibodies
 - Composed of 5000 to 50,000 atoms

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Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
 - Larger, complex, dynamic structures
 - Diverse populations of molecules
 - Not easily characterized
 - Complicated manufacturing
 - Example: Teplizumab (Tepzetta)
- Small Molecule Drugs
 - Synthetic
 - Manufactured using a defined chemical process
 - Smaller and simpler
 - Example: Aspirin

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Size and Complexity of Biologic Drugs

Size & Complexity – Small Molecule Drugs & Proteins

	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size	Aspirin 225 atoms	IGG 150,000 atoms	IgG Antibody 250,000 atoms
Complexity	Bike 20 lbs	Car 3000 lbs	Business Jet - 10,000 lbs (aircraft)

<https://www.usabio.com/press/molecules-compared-biologics-and-the-bioinjection-debate>

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Making Biologics

A piece of DNA is inserted into a living cell—yeast, bacterial, viral, or mammalian cell

↓

Cell then produces a large amount of a specific molecule (e.g. protein)

↓

Desired molecular isolation (living cells/material removed - only the desired molecules are left)

↓

The isolated molecules become the active ingredient in a biologic drug

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Treatments for Choroidal Neovascularization (CNV)

- ~ Where it 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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Past 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 - 2009
 - AMD
 - Ranibizumab (Lucentis)
 - Humanized monoclonal antibody fragment - 2006
 - AMD, DME, DR, RVO
 - Aflibercept (Eylea)
 - Fusion protein - 2011
 - AMD, DME, DR
 - Brodalumab (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 (brodalumab)

- ~ 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 intracocular 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
 - Intracocular inflammation (ICI) - 4.6% (n=50)
 - ICI + retinal vasculitis - 3.3% (n=36)
 - ICI + retinal vasculitis -retinal (artery) vascular occlusion - 2.1% (n=23)
 - Vision loss of 15 letters or more - <1%



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Eylea (aflibercept)

- ~ Regeneron Pharmaceuticals, Inc
- ~ Eylea 2 mg versus Eylea HD 8 mg
 - November 18, 2011 - Wet AMD (BLA)
 - July 29, 2014 - Diabetic Macular Edema
 - October 6, 2014 - Macula edema from retinal vein occlusion
 - May 25, 2015 - Diabetic retinopathy
 - August 17, 2018 - New Eylea (BLA) - wet AMD
 - May 13, 2019 - Diabetic retinopathy (BLA)
 - February 8, 2023 - ROP
 - Treatment of retinopathy of prematurity (ROP) in preterm infants
 - First pharmacological treatment for ROP in infants
- Mechanism of action: vascular endothelial growth factor A (VEGF-A) and placental growth factor (PlGF) antagonists that stops the growth of abnormal blood vessels and leakage in the eyes in patients diagnosed with retinal diseases

Biologics License Application (BLA) supplemental Biologics License Application (sBLA)

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Eylea (aflibercept)

August 18, 2023 at 8:05 PM EDT

+ Back

EYLEA HD (AFLIBERCEPT) INJECTION 8 MG APPROVED BY FDA FOR TREATMENT OF WET AGE-RELATED MACULAR DEGENERATION (wAMD), DIABETIC MACULAR EDEMA (DME) AND DIABETIC RETINOPATHY (DR)

Approval based on the pivotal PULSAR and PHOTON trials in which EYLEA® HD demonstrated clinically equivalent vision gains to EYLEA (aflibercept) injection 2 mg that were maintained with fewer injections

First and only treatment approved in wAMD and DME for immediate dosing at 8-week and up to 16-week intervals following three initial monthly doses

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Eylea (aflibercept)


- Now have five approved indications to treat retinal conditions caused by ocular angiogenesis
- Wet AMD
- DME
- Macular edema following retinal vein occlusion (RVO)
- DR
- ROP

- Eylea HD 8 mg
- Wet AMD
- DME

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Vabysmo (faricimab-svoa)


- Genentech
- Indications: February 2022
 - Wet age-related macular degeneration (AMD)
 - Diabetic macular edema (DME)
- Indications: October 2023
 - Treat macular edema following retinal vein occlusion.
- Mechanism of action: vascular endothelial growth factor (VEGF) and angiotensin 2 (Ang-2) inhibitor
- Administration: Intravitreal injection
- Extended dosing 1-4 months



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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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Xdemvy (lotilaner ophthalmic solution) 0.25%

- Tarus Pharmaceuticals
- Indication: Demodex blepharitis
- Mechanism of action: lotilaner works as an antiparasitic agent to target parasite-specific GABA-Chloride (Cl) channels
 - Located within the nervous system channels of the Demodex mites
- Administration: Drops
- Dosing: 1 gtt BID x 6 weeks

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45-Year-Old White Man Somewhat Symptomatic October 30, 2023

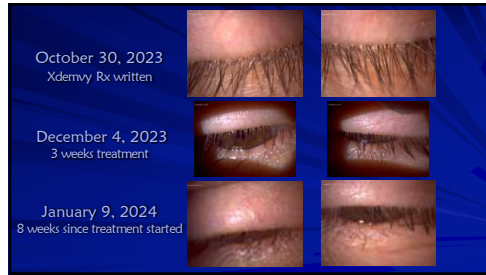


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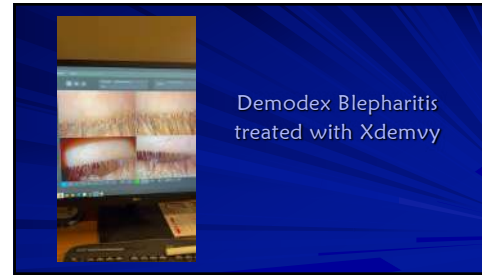
October 30, 2023 - December 4, 2023 5 weeks



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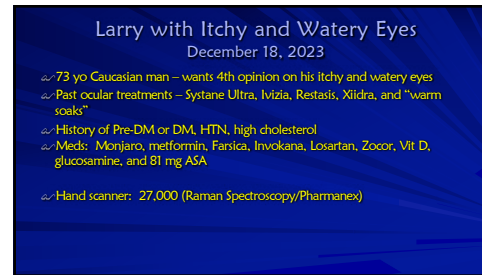
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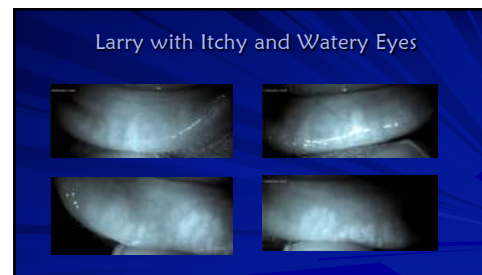
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Larry with Itchy and Watery Eyes


Treatment:

- Lengthy discussion on his complex ocular surface issue
 - Systemic association
 - Environment involvement
 - IBS microbiome dysfunction/dysbiosis
 - Nutritional association
- Rx Xdemvy
- Rx LifePak and Marine Omega
- Continue Ivizta
- Schedule for IPL



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December 18, 2023
Xdemvy Rx written
Importance of looking down



January 22, 2024
12 days S/P IPL
3 weeks Xdemvy treatment
4 weeks on LP and MO
Hand scan: 32,000



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IPL: 1-10-24, 2-7-24, 3-5-2024

Before 1-10-24 Treatment Before 2-7-24 Treatment



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IPL: 1-10-24, 2-7-24, 3-5-2024

Before 2-7-24 Treatment Before 3-5-24 Treatment



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Staff Asks How Is It Going?



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Do You Think Nutrition Played a Role?




Hand Scan: 42,000

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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^{1,5}
 - Demodex mites are associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis, perioral and scalp hair loss, and basal cell carcinoma^{1,6,7}
- Demodex folliculorum and Demodex brevis are the only 2 species found in humans⁸
 - The life cycle of the Demodex mite is approximately 14 to 18 days from the egg to the full stage followed by the adult stage⁸
 - The life span of the mite is limited outside the living body; direct contact is required for transmission⁸

D. folliculorum

0.3-0.4 mm length
Covers the base of the lash follicle⁸

D. brevis

0.1 mm length
Covers the meibomian gland⁸

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DEMODEX BLEPHARITIS | MECHANISMS OF DISEASE

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^{1,3}

BACTERIAL

- Demodex mites can contribute to blepharitis by carrying bacteria on their anterior surface that may elicit immune responses^{1,6,7}

CHEMICAL

- Demodex mites have been associated with altered meibum composition⁹
- Debris from Demodex mites can potentially lead to chronic inflammation and degeneration of conjunctival tissue⁸

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CLINICAL MANIFESTATIONS OF DEMODEX BLEPHARITIS

Disorders of Eyelashes^{1,2}

Involvement of the lash follicles can result in colobiasis and may lead to misdirection, trichiasis, and madarosis

Meibomian Gland Dysfunction^{1,3}

Blockage leads to filling, swelling, and many discharge products (crusts)

Lid Margin Inflammation^{1,4}

Severe lid margin inflammation can be caused by Demodex infestation and is delayed but otherwise spontaneously resolvable

Conjunctival Inflammation^{1,5}

Without proper hygiene, lid margin inflammation may spread over to the conjunctiva producing a condition known as blepharitisconjunctivitis

Corneal Manifestations^{1,6}

D. brevis is primarily associated with inflammation that spreads to the cornea, causing light-scattering corneal lesions, superficial vascularization, marginal ulcers, epithelioid-like lesions, keratic, and other deeper lesions

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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 10 mites per lash
 - >20 colobiasis on the upper eyelid
 - All local meibum (crusts)

Common symptoms that were frequently bothersome[†]:

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

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

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MECHANISM OF ACTION OF Xdemvy (Lotilaner Ophthalmic Solution 0.25%)

Xdemvy - 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 reside¹

Product form³
Preserved (sortate) multidose eye drop solution in bottle

Dosing⁴
Twice daily for 6 weeks

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Xdemvy 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 st collarette cure, 2 nd mite eradication, 2 nd redness + collarette cure
Safety Goal	Well-tolerated safety profile

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Rinsada

- ~ Biofilm does not stop at the lid
- ~ First in class to remove past the lid margin
 - * Bulbar, palpebral conjunctiva & fornix
- ~ Power wash the biofilm - ports of high-pressure irrigation
- ~ **72%** reduction in MMP-9
 - * Lasted 12 weeks
- ~ 4.33 improvement on visual analog scale

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Palpebral conjunctiva & fornix Not Discussed Anatomical Areas of the Ocular Surface

Compositional Fornix

- Main lacrimal gland ducts
- Accessory glands of Krause

Aqueous output

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Palpebral Conjunctiva & Fornix Not Discussed Anatomical Areas of the Ocular Surface

Palpebral Composition

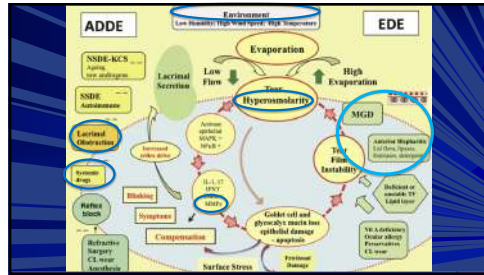
- Accessory glands of Wolfring
- Antigen presenting cells
- Mit cells
- Lymphocyte Cells
- Goblet Cells

Mediator Inflammatory reactions
Aqueous & meibom output

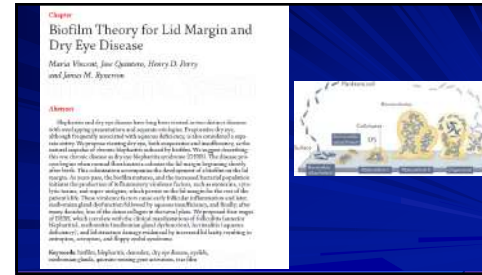
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The diagram illustrates the relationship between environmental factors (ADDE: Air, Dust, Dryness, etc.) and ocular surface health (EDE: Eye Discomfort, etc.). It shows how evaporation leads to tear hyperosmolarity, which triggers a cascade of events including lacrimal secretion, goblet cell dysfunction, and surface stress, ultimately leading to tear film instability and ocular surface disease.

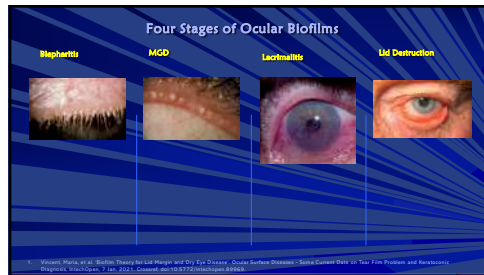
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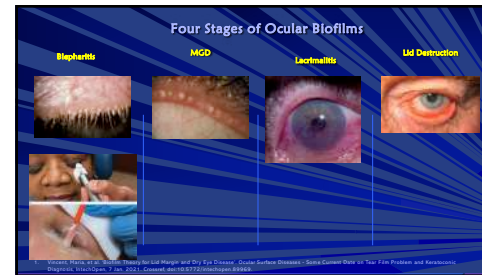
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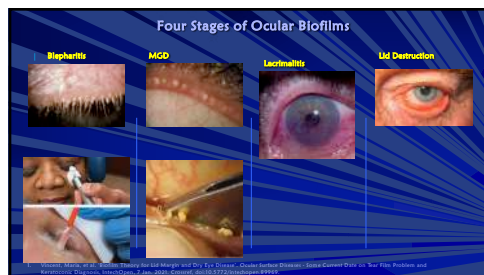
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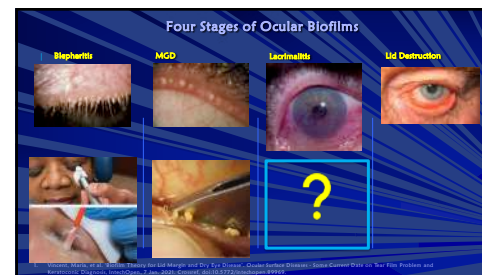
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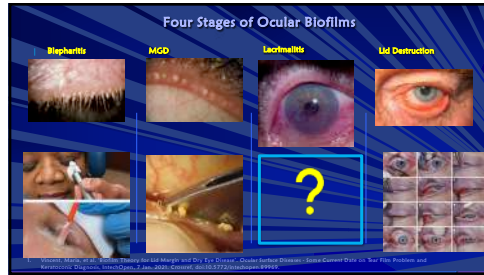
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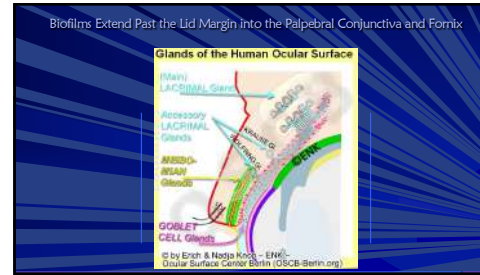
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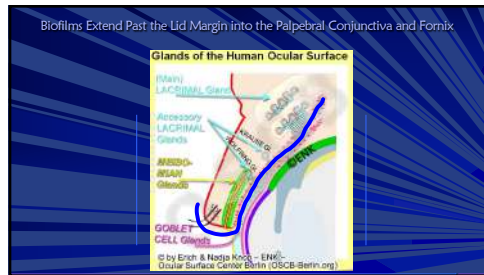
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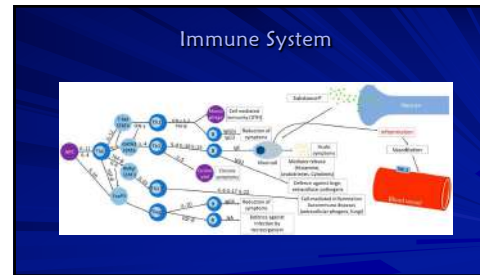
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An Excellent Tolerability Profile

IN 2 PIVOTAL CLINICAL STUDIES OF >1200 PATIENTS (>600 TREATED WITH MIEBO)

- 0 Serious ocular AEs
- 0.2% Low rate of discontinuation due to AEs
- 0.3% Low rate of burning or stinging on instillation
- 2.1% There was one ocular AE with an incidence 3.2% (blurred vision)

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MIEBO Offers a Comfortable Experience

In clinical studies, the majority of patients rated MIEBO as **COMFORTABLE OR VERY COMFORTABLE** on instillation*

- Small drop size (10 µl) means **MIEBO may feel different** from formulations containing water†
- There may be **no ocular sensation or blink reflex** upon instillation

Contact lenses should be removed prior to and for at least 30 minutes after the administration of MIEBO.

*Based on data from a clinical study comparing MIEBO (n=1200) and MIEBO (n=1200) with MIEBO (n=1200) and MIEBO (n=1200). Mean patient comfort score was 8.8 for MIEBO and 8.4 for water. 81% of patients treated with MIEBO reported a score of 8 or higher. †Formulations containing water may have a typical drop size of 25 to 50 µl.

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Veveye (cyclosporine ophthalmic solution) 0.1%

- ~ Narrow - Imprints
- ~ June 2023 - approval
- ~ Indication: Treatment of the signs and symptoms of dry eye disease (DED)
- ~ Mechanism of action: Calcineurin inhibitor immunosuppressant is meant for topical ophthalmic use
- ~ Vehicle: Perfluorobutylpentane (MOD)
- ~ Unique properties:
 - No pH or osmolality characteristics
 - Water-free
 - Preservative free
 - Low surface tension - rapid spreading
- ~ Administration: drops
- ~ Dosing: 1 gt BID
- ~ Drop size: **10 microliters**
- ~ Results: Day 29 significantly improved the signs of DED

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Nanodropper

- ~ Most eye drops are 30-60 microliters
- ~ Current eyedrop bottles dispense about five times the liquid your eye can absorb
- ~ Up to 80% of every drop is wasted due to overflow onto your cheek
- ~ Drainage by the tear ducts where the medication is absorbed into the rest of your body
- ~ Decades of clinical research has shown that smaller drops are as effective
- ~ Many cases, safer than current drops
- ~ Nanodropper is the only FDA-listed - volume-reducing adaptor for eyedrop bottles
- ~ Twist the Nanodropper onto a compatible bottle

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Nanodropper – microliters?

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Cequat™ (cyclosporine ophthalmic solution) 0.09%

- ~ Sun Pharmaceuticals, Approved August 2018
- ~ Dosed BID
- ~ Single-use vials
- ~ "New Nanomicellar Ophthalmic Solution for Treatment of Keratoconjunctivitis Sicca"
 - Formulation technology uses micelles
 - Gelatinous aggregates of amphiphatic molecules
 - Hydrophobic and hydrophilic molecules
 - Ease of entry into conjunctiva and cornea
 - High delivery of cyclosporine A (C₁A)

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Cequa™ (cyclosporine ophthalmic solution) 0.09%

Indication and Important Safety Information

Indication:
A calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

Warnings and Precautions:
Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.
Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

Adverse Reactions:
The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (2.2%) and conjunctival hyperemia (6%).

Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

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Cequa™ Formulation

- Novel, aqueous, nanomicellar formulation of cyclosporine A 0.09%¹⁻⁴
- Unpreserved, isotonic, neutral pH fluid that is supplied in unit dose vials
- Well tolerated in a 12-week phase 2b/3 study⁵

1. Chakrabarti et al. Invest Ophthalmol Vis Sci. 2012;53(12):3611-3617. 2. Nishida et al. J Control Release. 2012;164(1-2):1-11. 3. Vedula et al. Invest Ophthalmol Vis Sci. 2014;55(12):7442-7447. 4. Chakrabarti et al. Invest Ophthalmol Vis Sci. 2014;55(12):7448-7453. 5. Thakur et al. Invest Ophthalmol Vis Sci. 2014;55(12):7454-7459.

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Effect of Cequa Cyclosporine Ophthalmic Solution 0.09% in Patients With Dry Eye Disease That Is Inadequately Controlled on Cyclosporine 0.05% Ophthalmic Emulsion

Phase 4 Study Results

- Objective: To evaluate improvement in DED signs and symptoms following use of CcA 0.09% in patients whose DED is inadequately controlled on CcA 0.05%.
- A total of 124 patients were included in the ITT population (received ≥1 dose of study drug and had ≥1 postbaseline assessment).
- Mean ± SD patient age was 65.6 ± 11.54 years.
- Most enrolled patients were female (109; 87.9%).

CcA 0.09% elicited statistically significant improvement from baseline in total CFS (corneal fluorescein score) by 4 weeks of treatment
CcA 0.09% elicited statistically significant improvement from baseline in mSANDe (symptoms) score by 4 weeks of treatment
CcA 0.09% elicited statistically significant improvement from baseline in central CFS score by 4 weeks of treatment
CcA 0.09% elicited statistically significant improvement from baseline in total conjunctival staining score by 4 weeks of treatment
CcA 0.09% elicited statistically significant improvement from baseline in Schirmer's score at Weeks 4 and 12 of treatment
CcA 0.09% elicited statistically significant improvement from baseline in frequency of artificial tear use by 4 weeks of treatment

94

Effect of Cequa Cyclosporine Ophthalmic Solution 0.09% in Patients With Dry Eye Disease That Is Inadequately Controlled on Cyclosporine 0.05% Ophthalmic Emulsion

Phase 4 Study Results

- CcA 0.09% was generally well tolerated, consistent with its established safety profile
- Overall, 58 patients (43.3%) reported ≥1 TEAE
- Most AEs (73.8%) were mild in severity
- The most common treatment-related AEs were instillation site irritation (12.7%) and instillation site pain (2.2%)
- All other treatment-related AEs occurred in <2% of patients

Conclusion

- Twice-daily administration of CcA 0.09% elicited statistically significant improvement in both total CFS and mSANDe scores in patients whose DED was inadequately controlled on CcA 0.05%
- Improvements were evident as early as Week 4 and continued to increase in magnitude through Week 12
- CcA 0.09% was well tolerated in this patient population

95

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

96

Loteprednol Etabonate Products

Ester Steroids

- Lotemax suspension 0.5%
- Alex suspension 0.2%
- Lotemax gel 0.5%
- Lotemax SM gel 0.38%
- Invelty suspension 1.0%
- Eysuvis suspension 0.25%

97

Eysuvis- loteprednol etabonate 0.25%

- ~ Kala Pharmaceuticals, now Alcon
- ~ Approved October 27, 2020
- ~ Nanoparticle-based Mucus Penetrating Particles (MPP)
- ~ Dry eye flares
- ~ 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”

98

Eysuvis - loteprednol etabonate suspension 0.25%

- ~ Mechanism of Action – “AMPLIFY Technology”
 - Allows drug to penetrate through tear mucin
 - Increased penetration into tissue, 3-fold to original loteprednol
- ~ Nanoparticle-based Mucus Penetrating Particles (MPP)
 - Mucus is a barrier for topical ophthalmic drug delivery
 - AMPLIFY 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

99

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

100

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 Cel 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
 - Invekyta is 0.01%

101

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

102

Submicron Formulation


LOTEMAX® Gel Particle Size
0.4-0.6 µm (0.15-0.23 µm)

LOTEMAX® SM Particle Size
0.3-0.6 µm (0.15-0.23 µm)

103

Tyvaya – 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



104

Normal and Dysfunctional Tear Film*

Normal Tear Film



Dysfunctional Tear Film



Proteins

- Lysozyme
- Secretory phospholipase A2
- Lipocalin
- Complement
- IgG
- IgA
- IgM
- IgE

Mucins

- Mucin 1
- Mucin 2
- Mucin 3
- Mucin 4
- Mucin 5B
- Mucin 6
- Mucin 7
- Mucin 8
- Mucin 9
- Mucin 10
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Lipids

- Ceramide
- Cholesterol
- Phospholipid
- Triglyceride
- Sphingolipid
- Glycerol
- Fatty acid
- Steroid
- Sterol
- Sterane
- Steroid nucleus
- Steroid ring
- Steroid side chain
- Steroid oxygen
- Steroid nitrogen
- Steroid sulfur
- Steroid phosphorus
- Steroid halogen
- Steroid metal
- Steroid non-metal
- Steroid other

Natural tears contain a complex mixture of lipids, proteins, mucins and electrolytes.¹

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

105

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.

TFOZ DEWS = tear film repair

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



106

Parasympathetic Nervous System Controls Tear Film Homeostasis

The trigeminal nerve is **accessible within the nasal cavity** and is activated 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!



107

Lacrimal Gland Postganglionic Innervation¹

- 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




108

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




Partial Agonist

α4β2



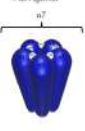
Moderate Agonist

α3β4



Full Agonist

α7




Human Nicotinic Acetylcholine Receptors

109

Tyrvaya – varenicline solution 0.03 mg

- Approved as **TYRVAYA**™ (varenicline solution) 0.03 mg October 13, 2021
- Cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease.
- Preservative-free, delivered as a 0.03 mL spray
 - One spray, each nostril, twice daily (approximately 12 hours apart)
 - 0.03 mg concentration | 28 mg/mL spray
 - 0.04 mg concentration | 28 mg/mL spray
- Onset of action and sustained outcomes demonstrated in clinical trials; sign outcomes measured at 5 minutes after nasal spray administration
- OC-3: 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 >10% of patients include cough, throat irritation, and irritation/sore (nose) irritation
- 0.34 mg/mL, C_{max} of 2 hours



110

Presbyopia This Market is Going Away Soon

- Presbyopia, the inevitable loss of near vision
- Research shows adults over 50 lose on average 15 lines of near vision per 6 years!
- Impact: **128 M** People in the US

Potential \$3B+ Market



111

Promise of a Once-Daily Eye Drop Solution is Welcomed By All Age Groups

Adapting Early	Busy Midlife	Active Aging
Seriously Consider 68%	Seriously Consider 62%	Seriously Consider 51%
4-7 days/week usage ¹ 80%	4-7 days/week usage ¹ 79%	4-7 days/week usage ¹ 79%
45-54	55-64	+65

Source: IQVIA commissioned survey of 1,200 professionals. 1/Percent of those who might seriously consider pil.1/2023

112

Vuity – Pilocarpine 1.25%

- AbbVie (was Allergan)
- Approved October 29, 2021
- Indication: adults with presbyopia
- MOA: Cholinergic muscarinic receptor agonist
- October 2021 – approved as QD dosing
- March 2023 – approved for BID dosing
- Warnings: Poor illumination and irrit. RD!
- Re-engineered design of pilocarpine, optimized concentration, pHast technology

113

All Pilocarpine formulations are stored at low pH to maintain stability¹⁻³

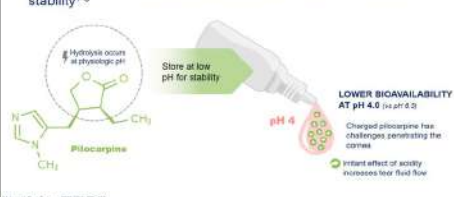
Hydrolysis occurs at physiologic pH

Store at low pH for stability

LOWER BIOAVAILABILITY AT pH 4.5 (vs pH 7.5)

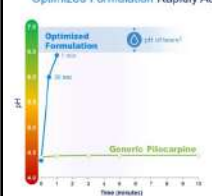
Charged pilocarpine has challenges penetrating the cornea

Irritant effect of acidity increases tear fluid flow



114

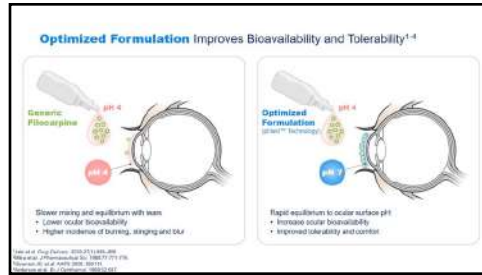
Optimized Formulation Rapidly Adjusts to Neutral pH After Administration



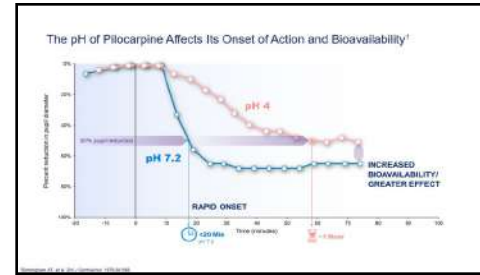
The Optimized Formulation with pHast™ Technology equilibrated to physiologic pH within 1 minute!

In vitro studies showed that the pH of Generic Pilocarpine did not reach physiologic pH in simulated tear fluid, even after 10 minutes!

115



116



117

Qlosi (pilocarpine hydrochloride ophthalmic solution) 0.4%

- Orasis Pharmaceuticals
- October 2023 – approval
- Pronounced: CLOHsee
- Indication: Treatment of presbyopia
- Dosing: one drop in each eye can be used daily or as needed
 - Dosing up to twice a day, 2 to 3 hours apart
- Low dose pilocarpine

118

Aceclidine-Based Eye Drop

- Not on the market**
- Unique MOA Profile**: Only moxifloxacin to achieve pupil sweet spot -0.8mm/0.9mm pupil
- Best-in-class clinical data**: 79%2-line and 92%2-line Near Vision improvement at 30min with +3.00 diopter
- Late Stage**: Ongoing Phase 3 trials for LND00 and LND01
- Market Exclusivity**: Broad IP protection and NCE status provide strong protection
- Proven successful team**: Experienced team backed by RA Capital, Alpha Wave Ventures, Venard Ventures, Section Asset Management, Point 72, RWJ and others

119

Mycombi
Tropicamide 1% and Phenylephrine Hydrochloride 2.5% Ophthalmic Spray

- Eyenova, Inc
- May 2023 - approval
- Spray
- Indication: For inducing mydriasis
- First-in-class, fixed-dose combo product of Tropicamide and phenylephrine
 - Designed to induce mydriasis during in-office diagnostic procedures and conditions that call for short-term pupil dilation

120

Ryzumvi (phenolamine ophthalmic solution) 0.75%

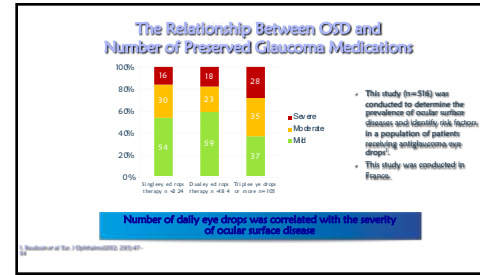
- Viatris
- September 2023 – approval
- Indication: treatment of pharmacologically induced mydriasis produced by adrenergic agonists
- Dosing: 1-2 gtt in the dilated eyes after the exam, 12 years or older
- Dosing: 1 gtt in the dilated eyes after the exam, 3-11 years old
- Mechanism of action: alpha adrenergic blocker, non-selected alpha-1 and alpha-2 adrenergic agonist – iris dilator muscle
- Rev-Eyes 2.0™ - no brow ache and improved redness

121

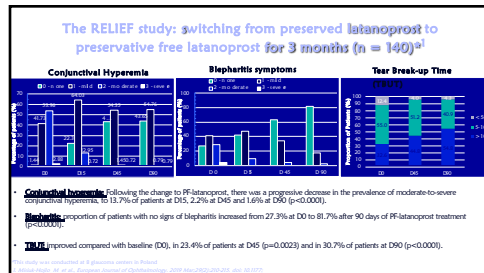
If you have a glaucoma practice you have an ocular surface disease practice

Fluorescein conjunctivitis
Superficial Punctate Keratitis (SPK)

122



123



124

Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

- Thera Pharma Inc
- December 2022 - approval
- Indication: treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT)
- First and only clinically proven formulation of preservative-free latanoprost currently available in the U.S.
- Dosage: single dosage to be placed in the eye(s) once daily in the evening
- Mechanism of action: prostaglandin F2α analogue

125

Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

- Launched in Europe as the first preservative-free latanoprost formulation in 2013
- Available in 46 countries including Canada
- PF-latanoprost formulation approved in the US is the same formulation used in Europe
- Can be stored at room temperature (15C - 25C, or 59F - 77F)

126

Background of Topical Ophthalmic Preservatives

- Preservatives provide important and necessary antimicrobial activity
- Crucial in maintaining sterility and extending the shelf-life of multi-dose formulations of topical ophthalmic medications
- Preservatives are toxic to the ocular surface, particularly in the setting of chronic, prolonged exposure
- As in patients with glaucoma who may have therapeutic regimens that involve multiple eye drops and frequent instillation
- Of all ophthalmic preservatives, benzalkonium chloride (BAK) is the most used and widely studied demonstrating significant ocular surface toxicity
- Although several classes of alternative preservatives have been developed
- All have varying degrees of ocular surface toxicity as well as efficacy profiles

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Cytotoxic Effects of BAK on Ocular Tissues

- Can occur at 0.005%, much lower than many of commercially used concentrations of BAK
- Cause tear film Disruption**
 - Acting as a detergent of the lipid layer of the tear film, decreases mucin production
- Induce Inflammation and cause damage to**
 - Trabecular meshwork
 - Corneal endothelial cells and Descemet's membrane
 - Corneal cells and increase in density
- Compromise glaucoma filtration surgery outcomes**
 - For each additional BAK preserved ophthalmic, the risk of early surgery failure increased by 25%
- Dose-dependent with cumulative burden of exposure**
 - Number of preserved medications, variable BAK concentration in each drop, dosing frequency per day and duration of therapy has been shown to correlate with ocular surface disease prevalence and severity in glaucoma patients and worse quality of life

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Preservatives in IOP Lowering Medications

BRAND NAME	ACTIVE INGREDIENT	PRESERVATIVE	OTC DROPS CONTAINING ALTERNATIVE PRESERVATIVES
OTC DROPS WITH BENZALKONIUM CHLORIDE (BAK)			
Brimonidine	Brimonidine 1.6%, 1%	BAC 0.01%	Alphagan P
Bimatoprost	Bimatoprost 0.03%	BAC 0.01%	Bimatoprost 0.03%
Brimonidine	Brimonidine 0.1%, 0.2%	BAC 0.01%	Trusopt IC
Timolol	Timolol 0.5%	BAC 0.02%	Timolol 0.5%, 0.2%
Latanoprost	Latanoprost 0.01%	BAC 0.02%	Trusopt Z
Travoprost	Travoprost 0.004%	BAK	Travoprost 0.004%
Netarsudil	Netarsudil 0.02%	BAC 0.02%	netAR
PRESERVATIVE FREE DROPS			
Alphagan	Brimonidine 0.1%	BAC 0.001%	Alphagan P
Carteolol	Carteolol 0.5%	BAC 0.001%	Carteolol 0.5%
Timolol	Timolol 0.5%	BAC 0.001%	Timolol 0.5%
Bimatoprost	Bimatoprost 0.03%	BAC 0.001%	PFI Latanoprost
Latanoprost	Latanoprost 0.01%	BAC 0.001%	Latanoprost 0.01%
Travoprost	Travoprost 0.004%	BAC 0.001%	Travoprost 0.004%
Netarsudil	Netarsudil 0.02%	BAC 0.001%	netAR
Puritan	Puritan 0.005%	BAC 0.001%	Puritan 0.005%
Yuzel	Latanoprost 0.01%	BAC 0.001%	Yuzel
Phoslo	Phoslo 0.01%	BAC 0.001%	Phoslo 0.01%
Mapin	Mapin 0.01%	BAC 0.001%	Mapin 0.01%
Trusopt	Trusopt 0.01%	BAC 0.001%	Trusopt 0.01%

BAK is the most used preservative in topical ophthalmic formulations

PFI-Latanoprost has been approved by the FDA for use in the United States.

129

Alternative Preservatives in Glaucoma Medications

- To reduce the cytotoxicity of BAK, several 'alternative preservatives' have been developed for antiglaucoma medications:
 - Benzododecinium bromide a quaternary ammonium compound
 - PURITE®; S.O.C (Stabilized Oxychloro Complex)
 - soZia®; ionic-buffered system (combination of boric acid, zinc, sorbitol, borate and propylene glycol) and functions as an oxidizing preservative
- Although these alternatives are considered less toxic than BAK, they still may exert negative impact on ocular surface:
 - PURITE (used in Alphagan® P) was shown to induce less corneal and conjunctival inflammatory damage!
 - soZia (used in Travatan Z®); study showed less toxicity compared to BAK?

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Iyuzeh (latanoprost ophthalmic solution) 0.005% Preservative Free

- PFI-Latanoprost had a similar IOP lowering efficacy to Xalatan in patients with POAG or OHT. The most common adverse reactions (5% to 35%) were conjunctival hyperemia, eye irritation, eye pruritus, abnormal sensation in eye, foreign body sensation in eye, vision blurred, and lacrimation increased.
- PFI-Latanoprost has demonstrated similar IOP lowering efficacy to Xalatan in patients with POAG or OHT with a decade long clinical experience.
- PFI-Latanoprost has been approved by the FDA, providing US eye care professionals with another treatment option in their glaucoma treatment armamentarium.

131

Vyzulta™ (latanoprostene Bunod) Ophthalmic Solution 0.024%

- Bausch & Lomb
- November 2, 2017, approved
- Indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
- Only nitric oxide releasing agent that targets both the trabecular meshwork and uveoscleral pathway to reduce IOP
- 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 inflammation etc pain
 - Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur

132

Nitric Oxide Plays Important Roles Throughout the Body and the Eye

Physiological functions of nitric oxide

Nitric oxide is a key regulator of numerous physiological functions in the body, including those in the eye.

133

Only VYZULTA® Releases Latanoprost Acid and Nitric Oxide to Reduce IOP

Once metabolized, VYZULTA increases outflow through the

- Uveoscleral pathway
- Trabecular meshwork

VYZULTA (latanoprost isomer) is metabolized into Latanoprost acid (prostaglandin analog) and Nitric oxide. Latanoprost acid targets the uveoscleral pathway, while Nitric oxide targets the trabecular meshwork.

134

Trabecular Meshwork Is the Primary Outflow Pathway in Healthy Eyes, Through Which 60% to 80% of Outflow Occurs

Endogenous nitric oxide regulates aqueous humor outflow by relaxing cells of the TM to lower IOP

- > Nitric oxide production is increased in the cells of the Schlemm's canal in response to elevated IOP²
- > Nitric oxide diffuses to and relaxes the TM to increase outflow and lower IOP³

In glaucoma, studies suggest that deficiency in nitric oxide may increase outflow resistance and lead to elevation in IOP

135

VYZULTA® Delivers Latanoprost Acid and Nitric Oxide to Lower IOP

Latanoprost acid increases interstice pressure, causing muscle fibers to relax. Nitric oxide inhibits Rho kinase, decreasing calcium signaling and increasing calcium signaling. Both actions lead to increased outflow of aqueous humor and decreased IOP.

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Rhopressa™ 0.02% (netarsudil ophthalmic solution)

Alcon Pharmaceuticals – was 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 releases TM¹, increases outflow^{1,2}
- NET inhibition reduces fluid production³
- ROCK inhibition lowers Episcleral Venous Pressure (EVP)¹

AR-13324 (netarsudil) acts on the trabecular meshwork, Schlemm's canal, and episcleral veins to increase outflow and lower IOP.

138

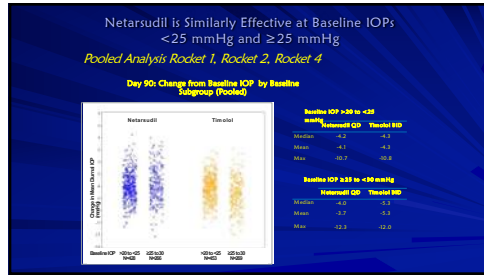
Rhopressa™ 0.02% (netarsudil) Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Microscopic images show TM expansion in donor eyes treated with netarsudil compared to control. The bar chart shows a significant increase in TM outflow facility with netarsudil compared to placebo.

Condition	Change (%)
vs. Baseline	~15
vs. Placebo	~25

139



140

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

141

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

Adverse Events	Netarsudil 0.02% QD (N=839)	Timolol 0.5% BID (N=839)
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.

142

Cornea Verticillata Observed in Phase 3 Studies

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

143

Cornea Verticillata Due to Phospholipidosis

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

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*

144

My Experience

OD treated OS gtt's


145

Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia	Corneal Verticillata	Conjunctival Hemorrhage
<ul style="list-style-type: none"> • 54.4% TEAE • Severity did not increase with continued dosing • Sporadic 	<ul style="list-style-type: none"> • 20.9% TEAE • Asymptomatic • 7.4% experienced reduced visual acuity • Not clear to a directly associated • All resolved after 13 weeks of D/C 	<ul style="list-style-type: none"> • 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 OCS – 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 Shovin, OD, FFAO

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Rocklatan™

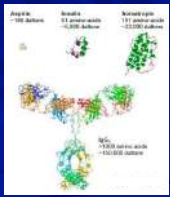
(netarsudil/latanoprost ophthalmic solution)
0.02%/0.005%

- Alcon Pharmaceuticals – was Aerie pharmaceuticals
 - March 14, 2019
- Once-daily eye drop
- First PCA combination approved
 - Superiority versus inferiority
- Refrigeration
 - Storage and after opening

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Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
 - Larger, complex, dynamic structures
 - Diverse populations of molecules
 - Not easily characterized
 - Complicated manufacturing
 - Example: Teplimumab (Tepessa)
- Small Molecule Drugs
 - Synthetic
 - Manufactured using a defined chemical process
 - Smaller and simpler
 - Example: Aspirin



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Why Your Patients Are on ELAHERE

Eye Care Considerations for Patients Treated With ELAHERE

151

Optometry's role with Elehere - Mirvetuximab Soravtansine gynx (MIRV)

- Antibody-drug conjugate (ADC) comprising an FR α -binding antibody, cleavable linker, and maytansinoid DM4 payload
- Primary ocular events with MIRV include corneal disorder, corneal epithelial defect, keratitis, keratopathy, corneal deposits, and punctate keratitis
- Exam and dear patient for treatment

152

Elehere - Mirvetuximab Soravtansine

Mirvetuximab soravtansine (MIRV) is the first biomarker-directed agent showing antitumor activity in patients with FR α -positive platinum-resistant ovarian cancer (PROG)

- MIRV is an antibody-drug conjugate (ADC) comprising an FR α -binding antibody, cleavable linker, and maytansinoid DM4 payload
- A phase 3 clinical study, SORAYA, evaluated MIRV in patients with FR α -high (PROG) who had received 1 to 3 prior therapies, including required bevacizumab

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Why Your Patients Are on ELAHERE

ELAHERE is a therapy approved to treat certain patients with advanced ovarian cancer

- ELAHERE is indicated for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Who have received one to three prior systemic treatment regimens
- This indication is approved under accelerated approval based on tumor response rate and durability of response

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Why Eye Care Is Important for Patients Receiving ELAHERE™

You play a critical role in patient management as ocular adverse events have been observed in patients treated with ELAHERE

BOXED WARNING: OCULAR TOXICITY

- ELAHERE can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis.
- Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated.
- Administer prophylactic artificial tears and ophthalmic topical steroids.
- Withhold ELAHERE for ocular toxicities until improvement and resume at the same or reduced dose.
- Discontinue ELAHERE for Grade 4 ocular toxicities.

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Proposed MOA for Ocular Events Associated With MIRV

- The underlying mechanisms of ocular toxicities remain poorly understood, but it is hypothesized to be an off-target effect on the corneal epithelium due to the lack of FR α receptors in that part of the eye
- Anti-microtubule payloads such as DM4 have been previously associated with resolvable ocular toxicity, such as blurred vision, dry eye, and keratopathy
- One hypothesis for toxicity seen with anti-microtubule payloads is that symptoms arise from a change in curvature of the cornea due to transient alterations in corneal epithelial thickness or corneal biomechanical properties, associated with the presence of microcyts
- Additionally, prolonged retention in circulation associated with MIRV's stable linker may lead to enhance exposure in normal tissue

The ocular AE profile of MIRV is a dose-dependent toxicity limited to the corneal epithelium of the eye, with resolvability observed in both non-clinical and human studies

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Microscopic Analysis of the Corneal Epithelium

Non-clinical Microscopic Analysis (Control and MIRV 12-mg/kg Dose)

Key Observations With MIRV 12-mg/kg Dose

- Fewer and larger epithelial cells
- Overall thinner epithelial layer
- Basal layer appearing disorganized as seen normal histology visible nuclei
- No visible nuclei in places across the thickness of the epithelial layer, suggesting no cells other than those of the basal layer were present
- Lesions only at the periphery of the cornea

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Due to the Possibility of Ocular Adverse Events With ELAHERE Eye Care Is Necessary

Ophthalmic Exams **Preventive Measures** **Lubricating Eye Drops** **Ophthalmic Topical Steroids**

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Proactive Management of Ocular Adverse Events

- Patients should receive a baseline ophthalmic exam from an ophthalmologist or optometrist prior to treatment initiation and follow-up exams during every other cycle for the first 8 cycles, and as clinically indicated
- Tell patients to avoid use of contact lenses, unless they are medically necessary
- Use of preservative-free* lubricating eye drops at least 4 times daily and as needed is recommended during treatment with ELAHERE
- Use of ophthalmic topical corticosteroids is recommended
 - The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp

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Recommended Schedule for Eye Drops

Ophthalmic Topical Corticosteroids

- Starting the day before ELAHERE infusion until 3 days after infusion (Days 1-4)**
 - Advise patients to apply 1 drop in each eye 6 times daily
- On Days 5-8**
 - Advise patients to apply 1 drop in each eye 4 times daily

Lubricating Eye Drops
The use of preservative-free lubricating eye drops is also recommended at least 4 times daily and as needed during treatment. Advise patients to wait at least 10 minutes after administering ophthalmic topical corticosteroids before using lubricating eye drops

160

What to Look for in the Baseline Ophthalmic Exam

- A baseline ophthalmic examination should include a visual acuity test and slit lamp exam
- Document the patient's current symptoms and visual acuity prior to the initiation of ELAHERE™

Symptom Assessment	Visual Acuity	Slit Lamp Exam
Inquire about ocular symptoms (eg, vision impairments, dry eye, photophobia, eye pain), and treat as appropriate	Measure best corrected visual acuity at baseline to help understand whether changes have occurred during follow-up exams	Assess corneal health (eg, keratopathy, superficial punctate keratitis) is recommended before initiation of treatment with ELAHERE

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What to Monitor During Scheduled Follow-up Ophthalmic Exams

Monitor patients every other cycle (every 6 weeks) for the first 8 cycles (<6 months) of ELAHERE™ for any changes from the baseline ophthalmic exam, and as clinically indicated*

Symptom Assessment†	Visual Acuity†	Slit Lamp Exam†
Inquire about any new or worsening ocular symptoms since the most recent ophthalmic exam	Compare against baseline measurement to determine whether best corrected visual acuity has changed	Document any ocular findings, including keratopathy and vesicles

Note: As part of their treatment with ELAHERE, your patient is being prescribed ophthalmic topical steroids that may elevate intraocular pressure.

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Presentation of Keratopathy (Microcyst-like Corneal Epithelial Changes)


- Microcyst-like corneal epithelial changes (MECs) may be identified during ophthalmic slit lamp exams
- MECs can appear in both symptomatic and asymptomatic patients?
- Document whether MECs are:
 - Confluent (ie, merging or clumped)
 - Nonconfluent (ie, separated or distinct)

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What to Expect With Ocular Events Associated With ELAHERE™


Integrated Safety Analysis of Patients Treated With ELAHERE (N=454)*

Timing of Onset




- Median onset to the first ocular adverse event was 5 weeks (range, 1 day-55.3 weeks)†

Impact



- Ocular adverse events of any grade occurred in 61% of patients†
- Grade 1 or 2: >90% of patients
- Grade 3: 5% of patients
- Grade 4: 0.2% of patients†

Resolution



- No patients had permanent ocular sequelae†
- Ocular adverse events led to permanent discontinuation of ELAHERE in 0.6% of patients†

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Monitoring Ocular Adverse Events


Ophthalmic Exam Findings Requiring Dose Modifications

Ophthalmic exam finding	Severity of finding	Action
Keratitis/keratopathy	Nonconfluent superficial keratitis	Monitor
	Confluent superficial keratitis, a cornea epithelial defect, or 3/6 or more loss in best corrected visual acuity	Notify treating oncologist†
Uveitis	Corneal edema or abnormal opacity or best corrected distance visual acuity of 20/200 or worse	Notify treating oncologist†
	Corneal perforation	Monitor
	Grade 3/4+ cell in anterior chamber	Monitor
	Grade 2/3+ cell or flare in anterior chamber	Notify treating oncologist†
	Grade 4 hypopycn	Notify treating oncologist†

Ocular adverse events should be treated by the eye care provider per standard clinical guidelines

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Coordinating With the Treating Oncologist



ELAHERE™ Ocular Assessment Form to Guide Ophthalmic Exams and Communicate With Treating Oncologists

- Reporting exam findings to the treating oncologist can guide the need for dose modification due to ocular events
- Dose reductions or modifications may help resolve ocular events
- Ocular adverse events led to permanent discontinuation of ELAHERE in 0.6% of patients

For questions or information about billing and coding, reference the ELAHERE Ocular Billing & Coding Guide



Scan this code to download a copy of the ELAHERE Ocular Assessment Form

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Oxervate™ (cenegermin-bkbj)

- ⚡ Dompé pharmaceutical 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
- ⚡ 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
- ⚡ ADRs: eye pain, inflammation, corneal deposits
- ⚡ Contraindications
 - None

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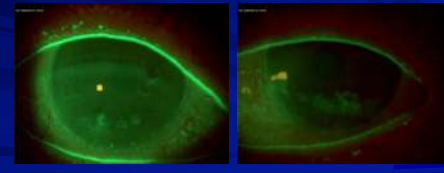
Stain Without Pain!

Actually, the OS is More Comfortable – What?

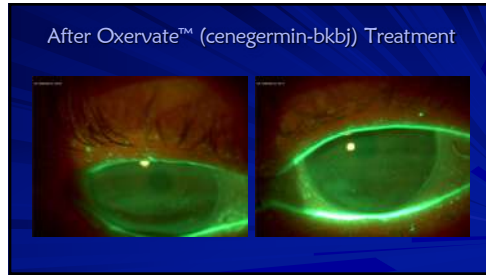


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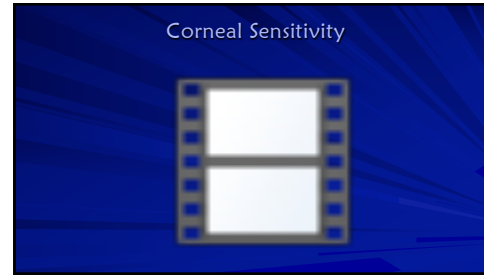
Before Oxervate™ (cenegermin-bkbj) Treatment



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171

Oxervate™ (cenegermin-bkbj)

- Grading corneal sensitivity: (Cotton Tip)
 - Normal
 - Reduced
 - Absent
- Reduced in all quadrants and centrally
- Absent inferior quadrant, reduced everywhere else

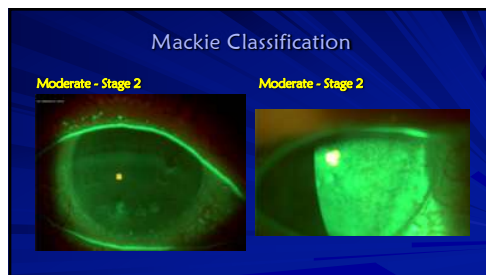
- Neurotrophic Keratitis: (Staining)
 - Mild - Stage 1
 - Moderate - Stage 2
 - Severe - Stage 3

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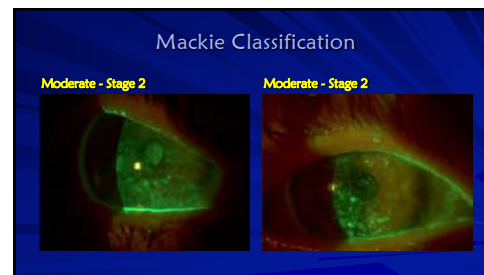
Neurotrophic Keratitis is a Degenerative Disease

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

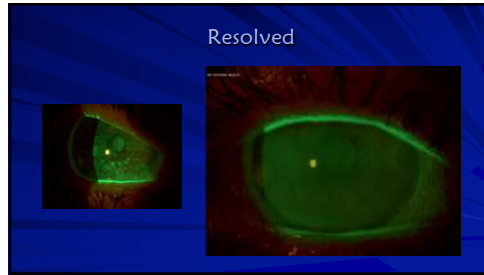
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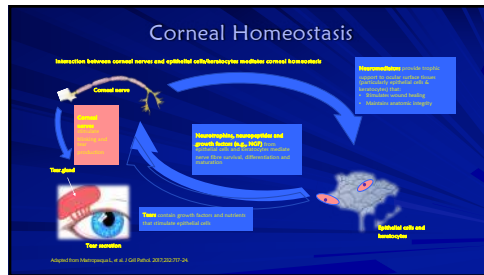
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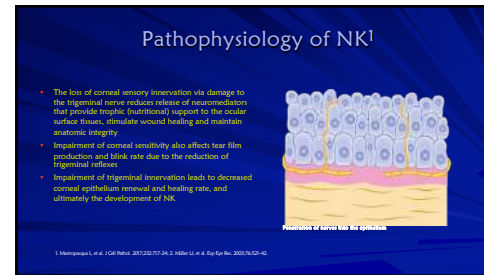
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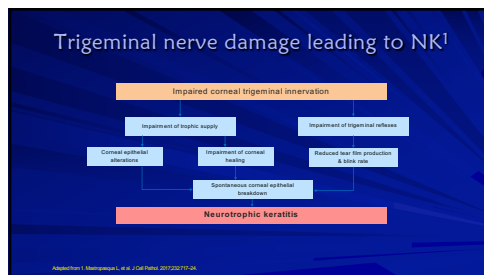
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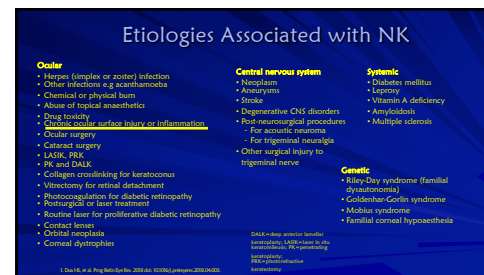
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NK classification

- Stage I: Mild** (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
- Stage II: Moderate** (Epithelial defect without stromal defects): Frank persistent epithelial defect and corneal hypo-sensitella/ anaesthesia
- Stage III: Severe** (Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-sensitella/ anaesthesia

1. Dua HS, et al. Prog Retin-Eye Res. 2018;61: 101706 | eprints.2018.101003. [Link absent at page 2]. 2. Dua HS, et al. Prog Retin-Eye Res. 2018;61: 101706 | eprints.2018.101003. [Link absent at page 2].

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Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis¹

Corneal sensitivity tests?

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

1. Dua HS, et al. Prog Retin-Eye Res. 2018;61: 101706 | eprints.2018.101003. [Link absent at page 2]. 2. Dua HS, et al. Prog Retin-Eye Res. 2018;61: 101706 | eprints.2018.101003. [Link absent at page 2].

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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:

- TEAR SECRETION:** NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion²
- CORNEAL INNERVATION:** NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory axons³
- CELL PROLIFERATION AND DIFFERENTIATION:** NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells⁴

1. Lashkarev A, Bora P, Bora S, Chugh G, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 2018;378:1313-1320. 2. Savelbergh G, et al. NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion. Invest Ophthalmol Vis Sci. 2011;52(12):7611-7618. 3. Lashkarev A, et al. NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory axons. Invest Ophthalmol Vis Sci. 2011;52(12):7619-7626. 4. Lashkarev A, et al. NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells. Invest Ophthalmol Vis Sci. 2011;52(12):7627-7634.

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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 neurons¹
- ↳ The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s²
- ↳ Cenegegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein³

1. Lashkarev A, Bora P, Bora S, Chugh G, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 2018;378:1313-1320. 2. Savelbergh G, et al. NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion. Invest Ophthalmol Vis Sci. 2011;52(12):7611-7618. 3. Lashkarev A, Bora P, Bora S, Chugh G, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 2018;378:1313-1320.

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

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials¹
- 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

1. Lashkarev A, Bora P, Bora S, Chugh G, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 2018;378:1313-1320.

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Cenegegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues

Cenegegermin Endogenous NGF

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

1. Lashkarev A, Bora P, Bora S, Chugh G, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 2018;378:1313-1320.

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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% (0.02 mg/mL) (3.5 package insert). Boston, MA: Denovon 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-bkbj) ophthalmic solution 0.002% was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe

50 clinical trial sites in Europe and the U.S.
Study NCF0212 (REPARC) (N=52 per group) European patients with NI in one eye. NCT01756456

72.0% Study NCF0214 (N=54 per group) US patients with NI in one or both eyes. NCT02227947

65.2%

80% Remained healed for one year*
*Based on REPARC, the study with longer follow-up.

Of patients who healed after one 8-week course of treatment...

Notes: The most common adverse reaction was eye pain following instillation which was reported in approximately 50% of patients. Other adverse reactions include: eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears.
† Based on Lerman A, et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Keratinocyte Growth Factor for Non-infectious Keratitis. Ophthalmology. 2018;125(10):2462-2470.
‡ OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (3.5 package insert). Boston, MA: Denovon 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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Humira™ (adalimumab)

- Company: Abbvie
- Approved July 2016
- Indication: uveitis
 - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
- Mechanism of action: binds to TNF and blocks its action in the body
- Dosage: subcutaneous injection
 - Recommended dose is 80 mg initial dose
 - Followed by 40 mg every other week starting one week after initial dose
- The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for "off-label" uses.

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Humira™ (adalimumab)

- Non-infectious intermediate, posterior and panuveitis
- Reason for reduced acuity?

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Humira™ (adalimumab)

Monitoring parameters:

- ★ Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to ACTIVE tuberculosis
- ★ Once Humira is initiated, watch for any signs or symptoms of infection...if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.

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Hadlima™ (adalimumab-bwwd)

Biosimilars

- ★ Hadlima (Adalimumab-bwwd)
 - Biologic agent SIMILAR to Humira
 - What is a "biosimilar" agent?
 - Remember what the FDA say about "biosimilars"

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Humira™ (adalimumab) Hadlima™ (adalimumab-bwwd)

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete disease warning.

SERIOUS INFECTIONS (S.I.S.):

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections such as histoplasmosis, and infections due to other opportunistic pathogens.
- Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.
- Perform test for latent TB, if positive, start treatment for TB prior to starting HUMIRA.
- Monitor all patients for active TB during treatment, even if latent latent TB test is negative.

MALIGNANCY (M):

- Leishmaniasis and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.
- Post-marketing cases of lymphoproliferative T-cell lymphoma (DLCL) a rare type of T-cell lymphoma, have occurred in children and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

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Actemra™ (tocilizumab)

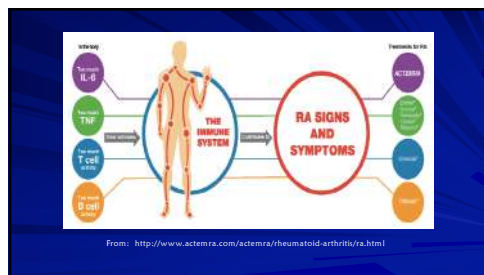
INDICATIONS:

- ACTEMRA is indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).
- ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.
- ACTEMRA is indicated for the treatment of active Crohn's disease (CD) in patients 18 years of age and older.
- ACTEMRA is indicated for the treatment of active pediatric Crohn's disease (CD) in patients 6 years of age and older.

ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Let's qualify this statement

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198

Actemra™ (tocilizumab)

Actemra™ (tocilizumab) - Genentec

- ★ First innovative therapy for CCA in more than 50 years
- ★ Design to speed the development for treatments of serious diseases such as CCA and certain cancers

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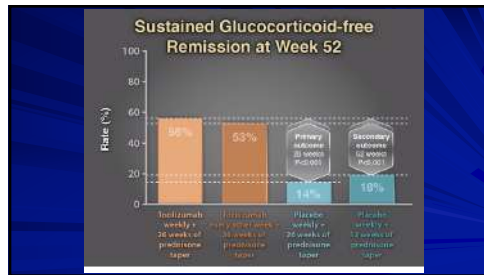
Actemra™ (tocilizumab)

- Patients were randomized to receive tocilizumab 162 mg weekly injections plus a 6-month and 12-month prednisone-taper compared to controls receiving placebo plus similar steroid taper
- The preliminary results indicate that patients receiving high dose tocilizumab had superior disease remission at 1 year compared to the steroid-only taper
- Further investigation from this study will attempt to identify the lowest therapeutic dose of prednisone that can be used in patients also using tocilizumab, the amount of tocilizumab needed to induce remission, and how long patients stay in remission on this therapy

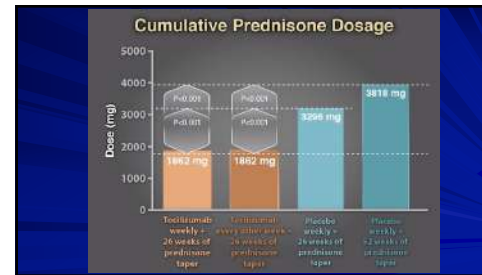
200

Tocilizumab	Placebo
Tocilizumab weekly + 26 weeks of prednisone taper (N=100)	Placebo weekly + 26 weeks of prednisone taper (N=50)
Tocilizumab every other week + 26 weeks of prednisone taper (N=50)	Placebo weekly + 52 weeks of prednisone taper (N=51)

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Actemra™ (tocilizumab)

- Tocilizumab does **not** directly treat GCA
 - Reduces steroid load after disease has been adequately treated by steroids and enhances disease remission
- Steroids are main therapy
- Studies are ongoing to see:
 - What is the lowest steroid tapering dose that can be used with tocilizumab
 - Future studies may show tocilizumab as steroid replacement

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Tocilizumab (Actemra)

WARNING: RISK OF SERIOUS INFECTIONS
 See full prescribing information for complete boxed warning:

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

205

Olumiant™ (baricitinib) and Rinvoq™ (upadacitinib)

- ~ Janus Kinase inhibitors
 - * Indicated for the treatment of adult patients with moderate/severe active rheumatoid arthritis
 - Must have failed 1 or more TNF-alpha inhibitors (e.g. Remicade, Humira)
- ~ THE HUB-BUB? It is an orally administered medication as opposed to MOST of the others that are injectables.
 - * Known as "un-jections"

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Family Medicine

- ~ **Aimovig™ (erenumab-aooe)**
- ~ **Ajovy™ (fremanezumab-vfrm)**
 - * Approved 2018
 - * Indicated for the PREVENTIVE treatment of migraine in adult patients
 - * Calcitonin gene-related receptor antagonist
 - SQ injection
 - Once per month for either product
 - Once every three months for Ajovy™
- ~ ADRs: constipation, injection site reactions

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Erenumab (Aimovig)

6.3 Constipation with Serious Complications
 Constipation with serious complications has been reported following the use of AIMOVIG in the postmarketing setting. There were cases that required hospitalization, including cases where surgery was necessary. In a majority of these cases, the onset of constipation was reported after the first dose of AIMOVIG; however, patients have also presented with constipation later on in treatment. AIMOVIG was discontinued to most reported cases of constipation with serious complications. Constipation was one of the most common (up to 7%) adverse reactions reported in clinical studies (see Adverse Reactions (6.2)).

Monitor patients treated with AIMOVIG for severe constipation and manage as clinically appropriate (see Patient Counseling Information (7)). The concurrent use of medications associated with decreased gastrointestinal motility may increase the risk for severe constipation and the potential for constipation-related complications.

6.4 Hypertension
 Development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the postmarketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalization. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of the cases, the onset or worsening of hypertension was reported after the first dose. AIMOVIG was discontinued in many of the reported cases.

Monitor patients treated with AIMOVIG for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of AIMOVIG is warranted if evaluation fails to establish an alternative etiology.

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Antibodies of Thyroid Dysfunction

- ~ **TSH Receptor Antibodies**
 - * Stimulating TSH receptor antibody
 - Thyroid Stimulating Immunoglobulin (TSI)
 - * Thyroid blocking antibody (TBAb)
- ~ **Thyroid Peroxidase Antibodies (TPOAb)**
 - * TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
 - * TPOAb contributes to thyroid cellular destruction
- ~ Most autoimmune thyroid dysfunctions have a combination of thyroid antibodies, however depending on which AB is more abundant results in the outcome of the disease

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Similar receptors are found in the skin, fat and muscle of the orbit

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You're in the Know

Normal Values
 Thyroglobulin 20 IU/ml
 Peroxidase <35 IU/ml
 TSI 1.75 IU/ml


It does work!

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Immunosuppression?

Biologics


- Immunosuppression biologics – suppress the immune system to get the effect
 - Remicade – “1st generation”
 - Chimeric molecule – mouse and human protein, a lot of sensitivity
 - Humira
 - Anti-TNF (RA and Crohn’s Disease)
 - Fully human protein, less sensitivity
 - Rituxan
 - CD 20 suppressor (B cell apoptosis)
 - Actively suppress the immune system
 - Immunomodulatory
 - Tepezza
 - IGF1R inhibitor
 - Full humanized monoclonal antibody
 - All the proteins are human – less to no sensitivity – more focused effect
 - Obtain fibroblasts to myofibroblast or adipocytes
 - Hyaluronic acid, glycosaminoglycan



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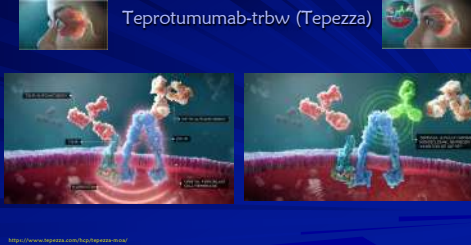
Teprotumumab-trbw (Tepezza)

- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
 - Chimeric Monoclonal Antibody
 - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
 - IGF1 (Insulin like growth factor I) and TSH receptor are over expressed
 - IGF1 receptor inhibitor monoclonal antibody
 - On the orbital fibroblasts:
 - Inhibiting downstream inflammatory cascade
 - Differentiation into adipocytes and myofibroblasts
- Phase 2 and published in New England Journal of Medicine
- Phase 3 completed
 - Not published
- PDUFA March 2020, was approved early in 2020



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Teprotumumab-trbw (Tepezza)



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Teprotumumab-trbw (Tepezza)

- Clinical Activity Score
 - Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
 - Scale of 7, needed 4 to be in the study
 - 78% improved to 0 or 1, 7% improved 0 or 1 with placebo
- Proptosis
 - Improvement of 2 mm or better
 - 83% had 2 mm or better, 10% with placebo
 - Average was 3.2 mm at week 24
- Diplopia
 - Scale of 0, 1, 2, or 3
 - 68% improved 1 point, 29% with placebo
- Grave’s Ophthalmopathy -Quality of Life Score
 - Scale 0-100
 - 17.28 point improved, 1.00 with placebo

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Teprotumumab-trbw (Tepezza)

- Infusion Reactions (mild/moderate): approximately 4% of patients
 - Transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain - will occur within 1.5 hours of an infusion
 - For those who have had a previous reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.
- Preexisting Inflammatory Bowel Disease: may cause an exacerbation of preexisting inflammatory bowel disease (“IBD”)
 - Monitor patients for flare; may require discontinuation of Teprotumumab (Tepezza)
- Hyperglycemia: increased blood glucose or hyperglycemia
 - In clinical trials, 10% of patients experienced hyperglycemia
 - Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab
 - Patients with preexisting diabetes should be euglycemic before beginning treatment

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Teprotumumab-trbw (Tepezza)

- Infusion center
 - Go to Horizon website
 - Contact Us
 - Type in your question
 - Looking for infusion center

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