Optometric Education Consultants

Herpes A to Z
for the Eye Care Provider

Greg Caldwell, OD, FAAO

Primary Eye Care Conference
Pittsburgh

Optometric Education Consultants

Saturday, February 17, 2024

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

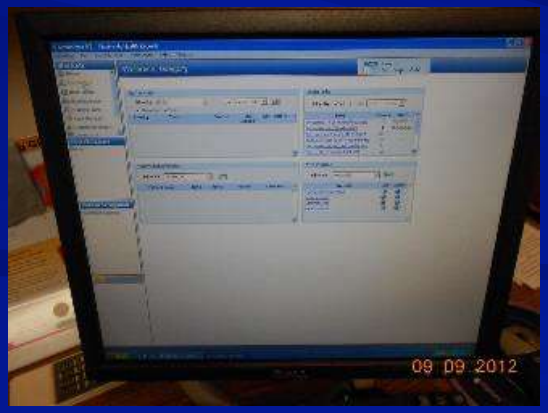
- Lectured for: Alcon, B&L, BioTissue, Dompé
  - Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, ImmunoGen, Iveric
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- 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

Optometric Education Consultants

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

Confidence
Capable
Courage
Commitment

Fun Facts About Herpes

- Are a leading cause of human viral disease
  - Second only to influenza and cold viruses
- There are more than 130 herpes viruses identified
  - 8 infect humans (9 if you count HHV-6A and HHV-6B as two separate)
  - 5 infect the eye
    - Herpes simplex 1
    - Herpes simplex 2
    - Varicella zoster
    - Epstein Barr
    - Cytomegalovirus
- USA 25% of the population is seropositive for HSV by 4 years old
  - Nearly 100% are seropositive by age 60
  - Lifetime prevalence of ocular manifestation in all HSV infected people is 1%

8 Humans- 5 Eye

Viruses of Humans	Common Name	Subfamily
Human herpesvirus 1	Herpes simplex type1	alpha
Human herpesvirus 2	Herpes simplex type 2	alpha
Human herpesvirus 3	Varicella-zoster	alpha
Human herpesvirus 4	Epstein-Barr	gamma
Human herpesvirus 5	Cytomegalovirus	beta
Human herpesvirus 6/7	exanthum subitum roseola infantum	beta
Human herpesvirus 8	Kaposi's Sarcoma-assoc.	gamma

Viruses of Humans	Common Name	Subfamily
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Human herpesvirus 4	Epstein-Barr	gamma
Human herpesvirus 5	Cytomegalovirus	beta
Human herpesvirus 6/7	exanthum subitum roseola infantum	beta
Human herpesvirus 8	Kaposi's Sarcoma-assoc.	gamma

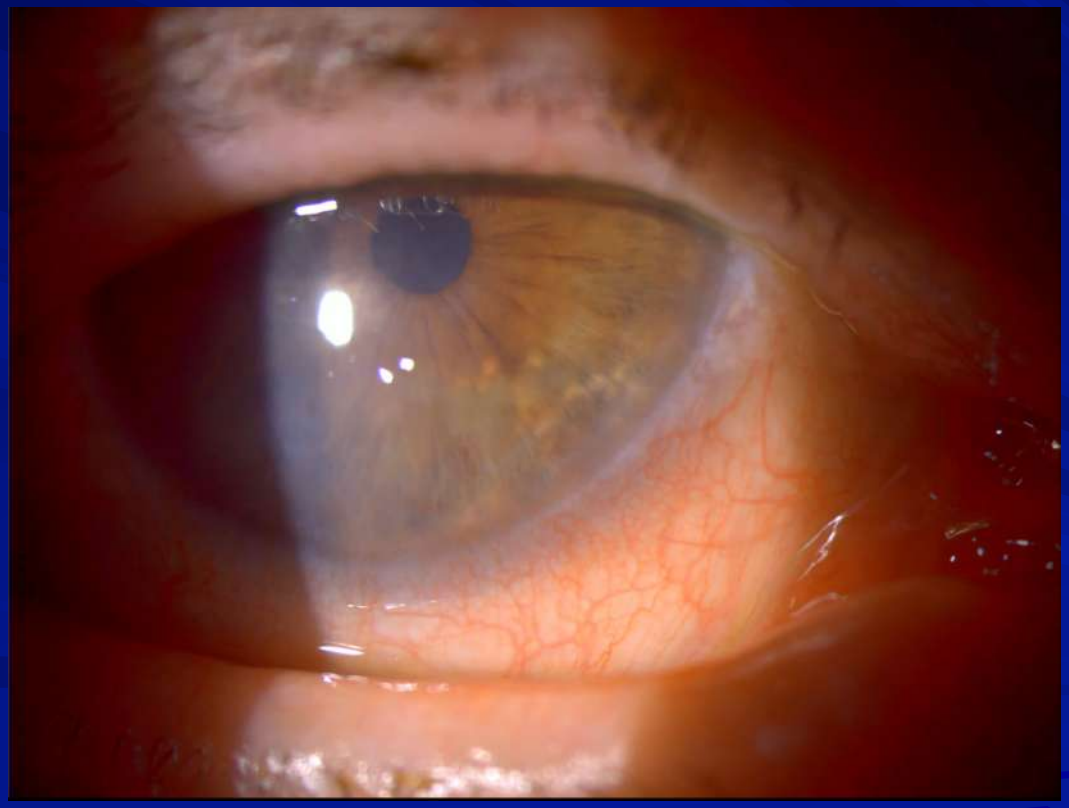
Herpes Simplex Virus Keratitis

- Is a leading cause of corneal blindness in the United States
  - Primarily caused by HSV-1 (65%)
- Keratitis nomenclature
  - Infectious epithelial keratitis
    - It's not critical to determine HSV 1 or 2
  - Stromal keratitis
  - Endotheliitis
  - Neurotrophic keratopathy
    - Serious complication

73-year-old woman

- Tuesday, 11-22-2022
- CC: OD possible clogged tear duct
  - Itchy inner part of the eye
  - Referred by patient's Primary Care Physician
    - Thinks clogged tear duct or infection
- On Friday, 11-18-2022
  - OD started to bother patient
  - Tried Visine with little or no help
- Meds: Cardizem, Eliquis, Trelegy, and Albuterol
- VA: OD 20/80 OS 20/30
- IOP: OD 10 OS 15 1:17 pm

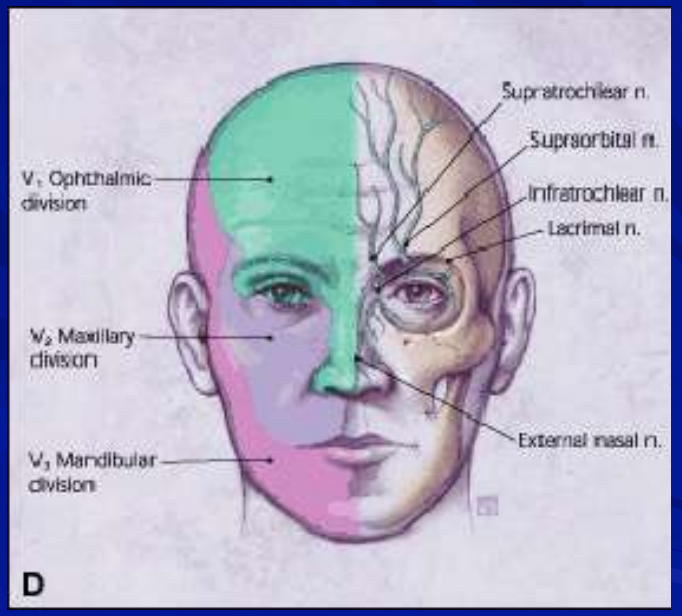
Chat Box: Evaluation and Treatment



Let's Hear from the Patient

Herpes Viruses are Classified by Their Location in the Latent State

Human herpes type	Name	Sub Family	Target cell type	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact usually sexual
3	Varicella Zoster virus (VSV)	Alphaherpesvirinae	Mucoepithelia	Neuron	Contact or respiratory route
4	Epstein-Barr Virus (EBV)	Gammaherpesvirinae	B lymphocyte, epithelia	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes and possibly others	Contact, blood transfusions, transplantation, congenital
6	Herpes lymphotropic virus	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Contact, respiratory route
7	Human herpes virus-7 (HHV-7)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma-associated herpes virus (KSHV)	Gammaherpesvirinae	Endothelial cells	Unknown	Exchange of body fluids?



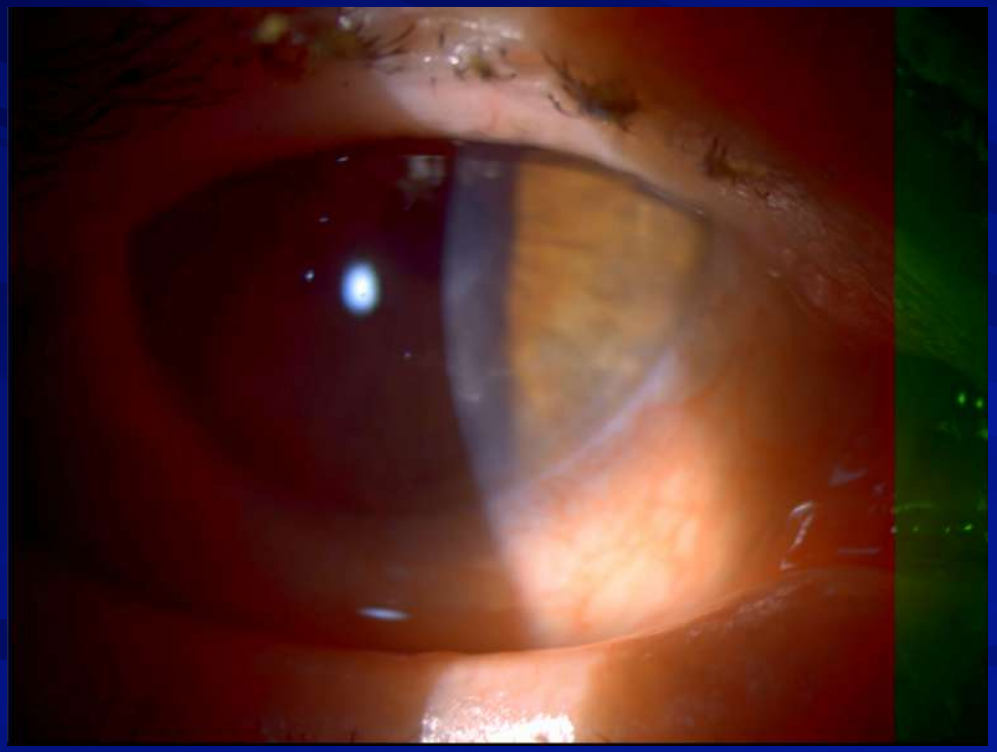
Treatment 11-22-2022

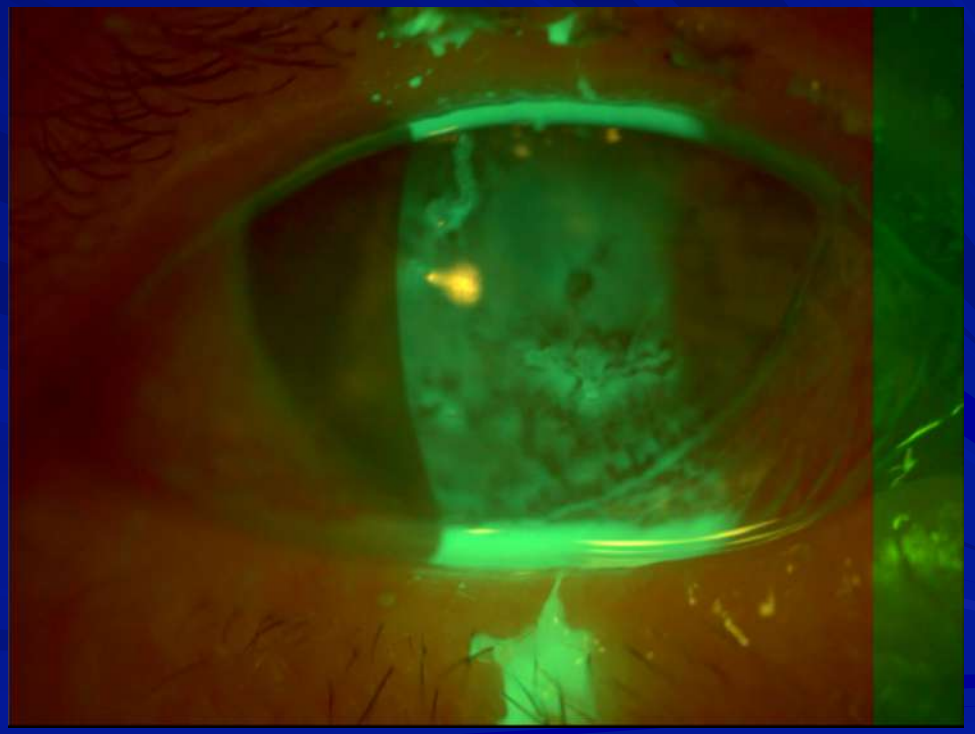
- Herpes Simplex Keratitis x 7 lesions
  - Educated patient on finding
  - Photo and video documents
  - Valtrex 1000 mg PO TID
  - Watch closely
  - Prokera not covered by insurance, patient declined Prokera
  - Add steroid at sign of reversal
  - RTC 1 day for HSV keratitis check

1 Day Follow UP 11-23-2022

- Feels slightly better
- VA: OD 20/70 OS 20/25
- Valtrex 1000 mg
  - 3 times yesterday
  - 2 today

1 Day Follow UP 11-23-2022





1 Day Follow UP 11-23-2022

- Improving
- Continue Valtrex 1000 mg PO TID
- Watch closely
- Photos and video documents
- Add steroids when reversal
- RTC in 2 days

3 Day Follow Up Friday 11-25-2022

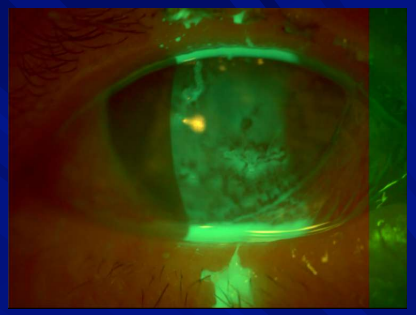
- Patient taking Valtrex as prescribed
- Reports watering over the last 2 days
- VA OD 20/70 OS 20/25
- IOP OD 11 OS 15

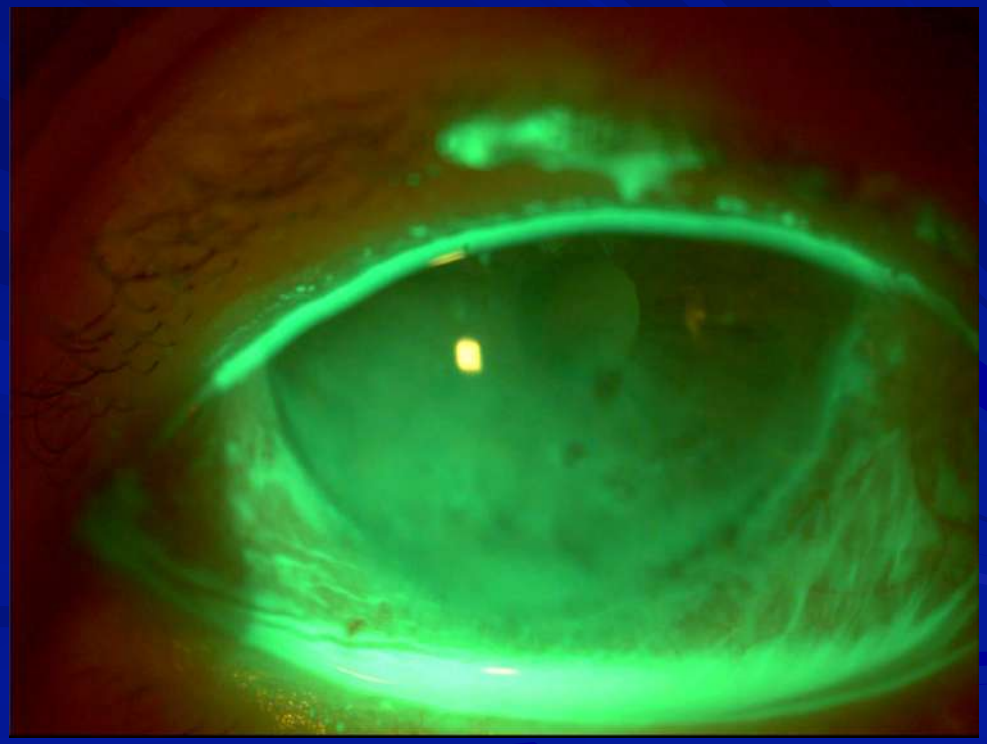
11-25-2022

11-23-2022

3 Day Follow Up Friday 11-25-2022

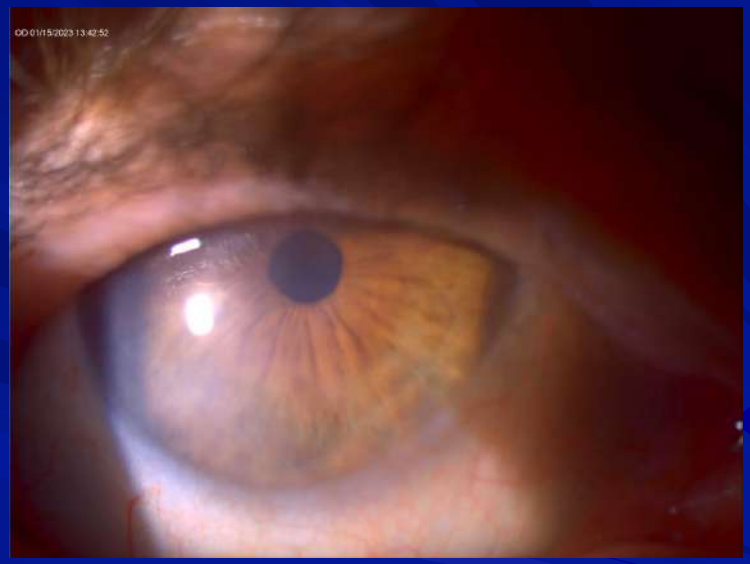
Time for steroid?





3 Day Follow Up Friday 11-25-2022

- Improving
- Responding to treatment
- Finish Valtrex PO
- Add loteprednol OD QID
- RTC 1 day, leaving town for weekend
- RTC Monday, gave patient my cell number



6 Day Follow Up Monday 11-28-2022

- Patient reports improvement since LOV
- Still some watering
- VA OD 20/70 OS 20/25
- IOP OD 15 OS 16

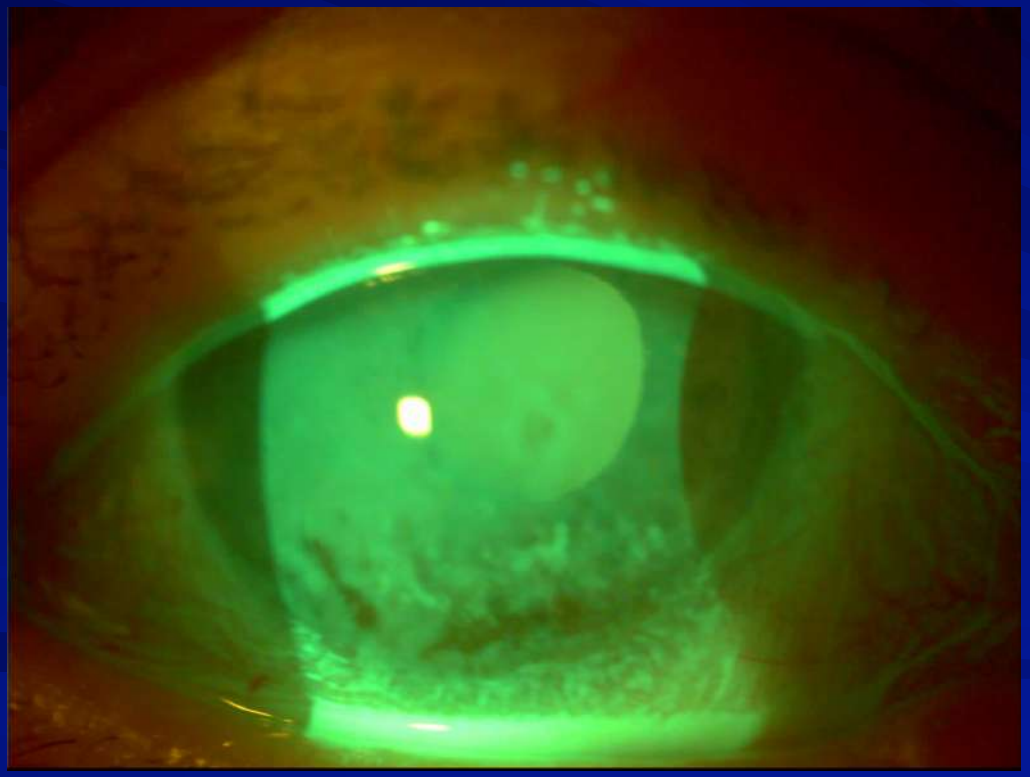
6 Day Follow Up Monday 11-28-2022

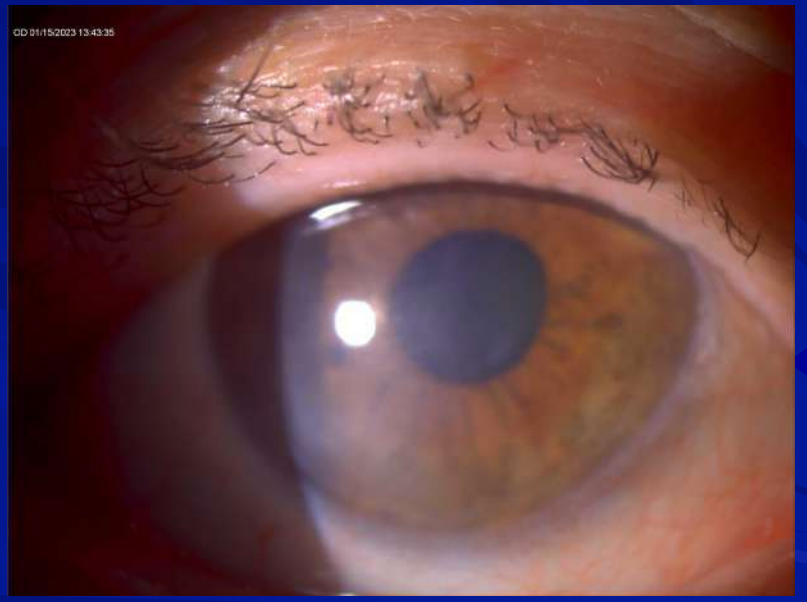
11-23-2022

11-25-2022

11-28-2022

6 Day Follow Up Monday 11-28-2022





6 Day Follow Up Monday 11-28-2022

- HSV 7 lesions improving and responding well to treatment
- Mild corneal haze
- Cataract OD limiting vision
- Finish Valtrex PO TID
- Continue loteprednol OD QID
- Recheck in 1 week

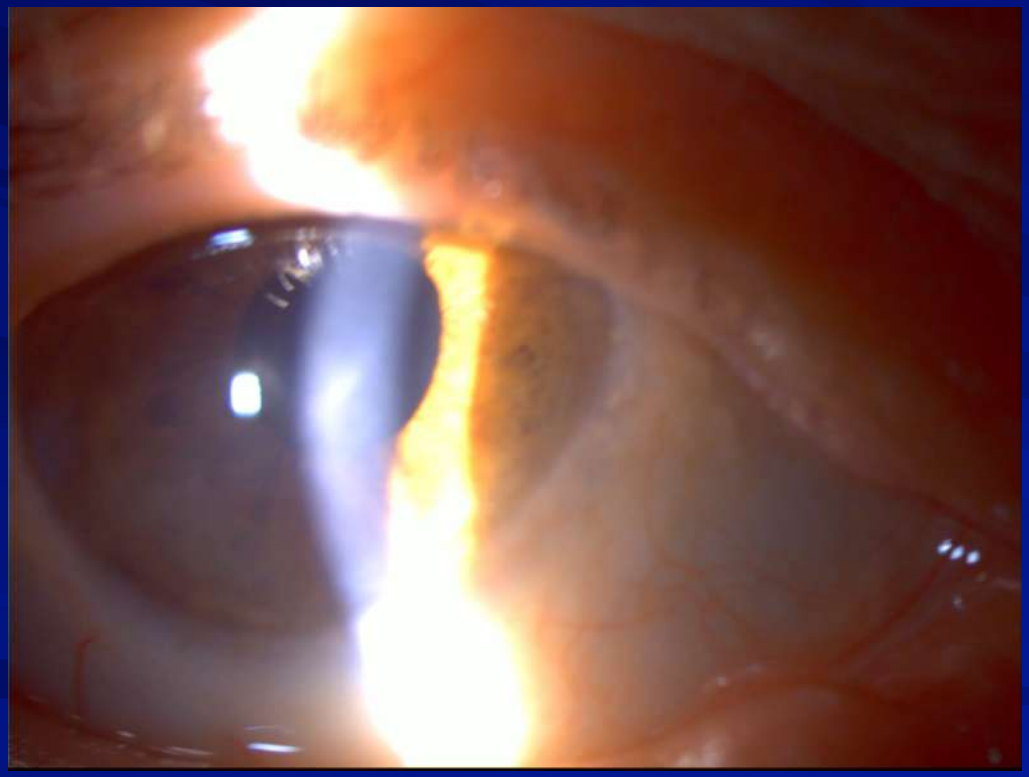
13 Day Follow Up Monday 12-05-2022

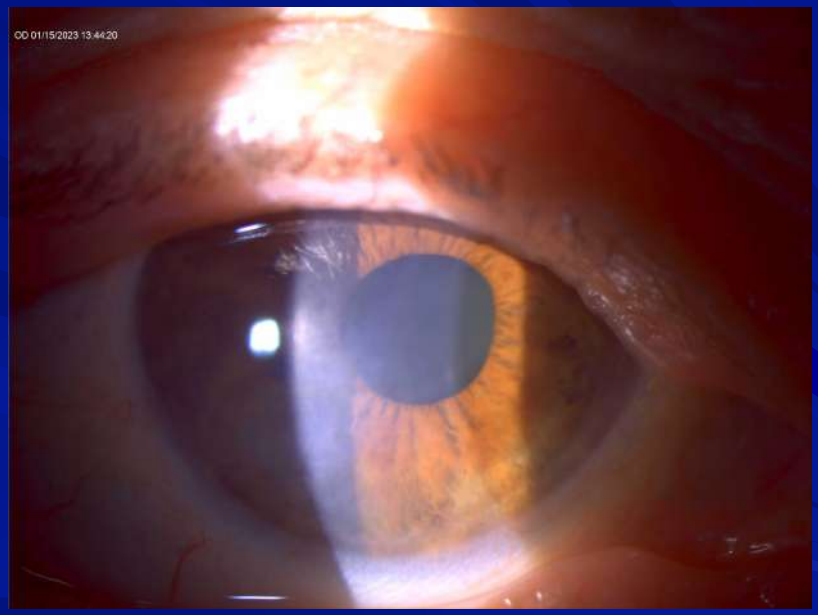
- Valtrex is finished
- Loteprednol OD QID
- Eye feels normal and no watering
- VA OD 20/60 OS 20/25
- IOP 14/14

12-05-2022

11-23-2022

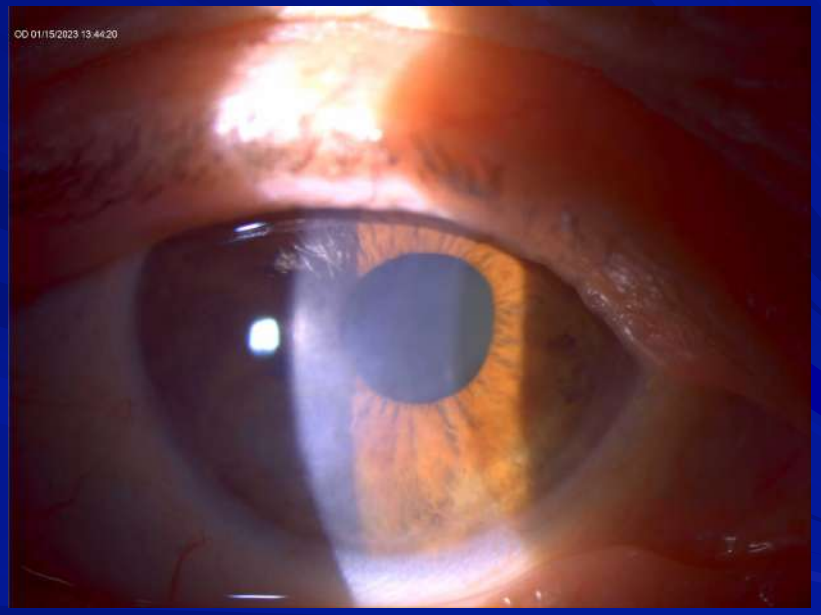
13 Day Follow Up Monday 12-05-2022





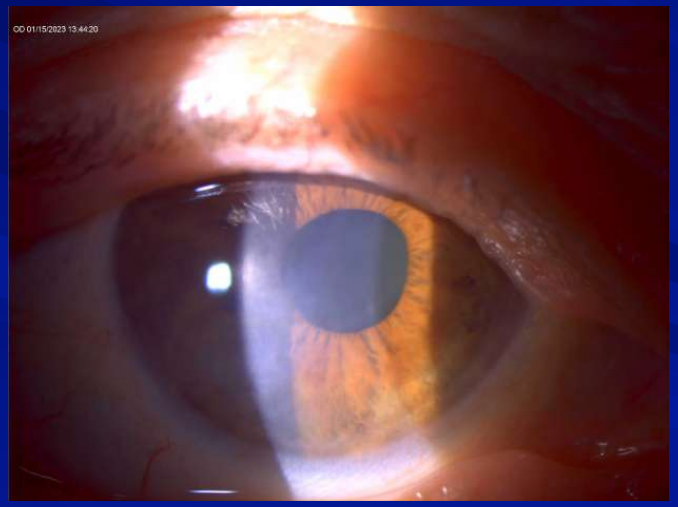
13 Day Follow Up Monday 12-05-2022

- 7 HSV lesions resolved
- Cornea haze and irregular cornea surface
  - Limiting BVA
- Loteprednol OD BID until bottle is empty
- RTC 1 month – consider cataract consult



6 Week Follow Up Wednesday 1-04-2023

- Valtrex and loteprednol finished
- VA: OD 20/40 OS 2025
- IOP 15/15
- Cornea haze minimum
- No iritis
- Nasal ectropion



- Tx: refer for cataract eval

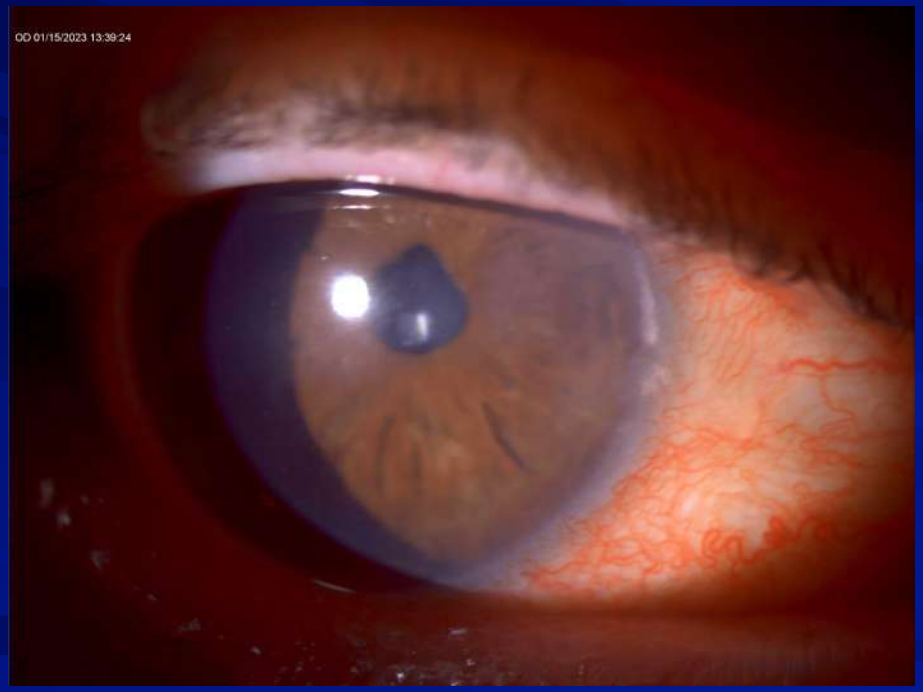
72-year-old white man

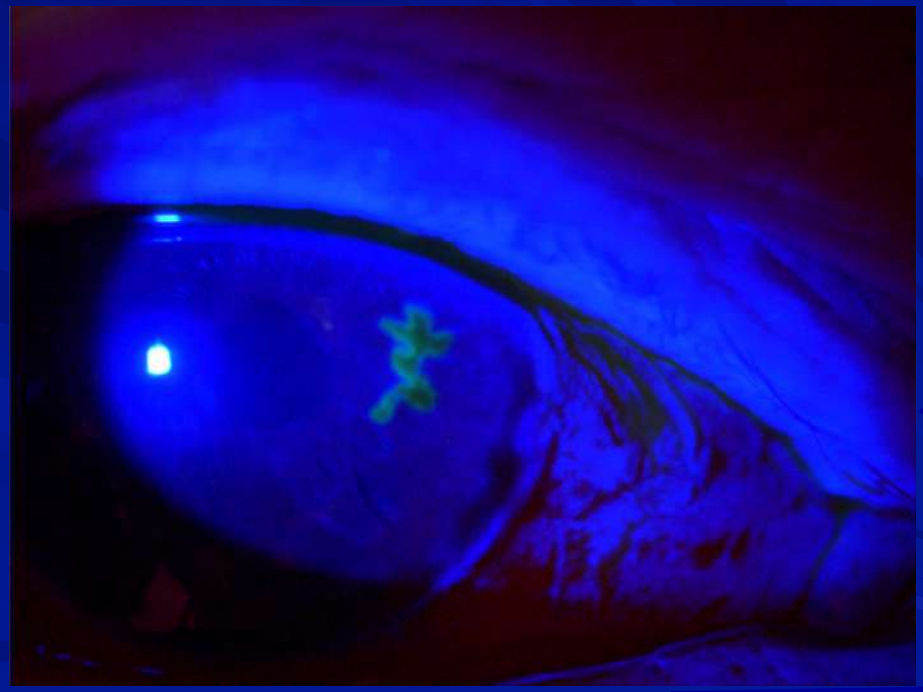
- First saw patient 6-26-2017
- History of herpes viral keratitis and cataract OD
- Wants opinion on keratitis and cataract

- VA: OD 20/100 OS Prosthetic
  - Saw at age 2 to OS
- Valtrex PO 500 mg
- Timolol OD QD
- Prednisolone OD QD
- IOP OD 18

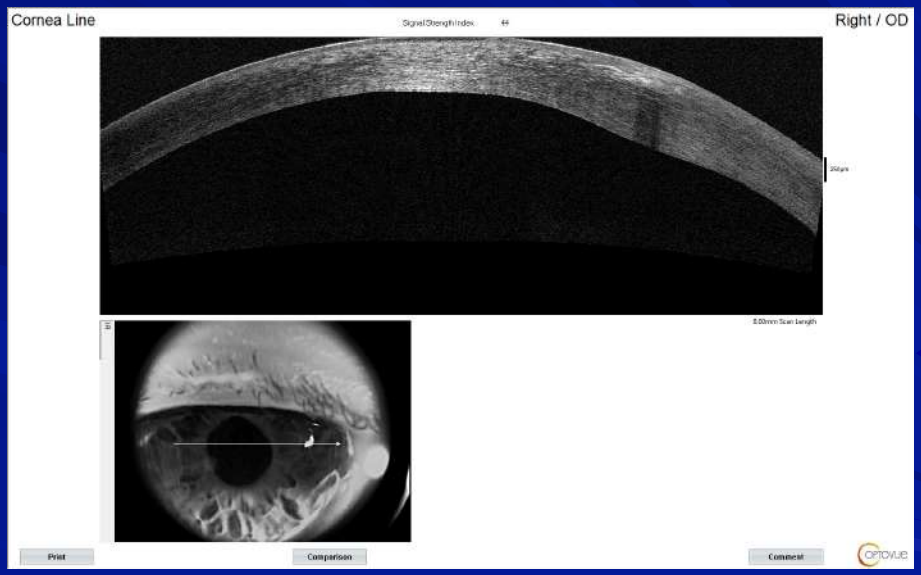
- Diagnosis: Monocular patient
  - Ocular HTN/Steroid responder
    - Good IOP
  - Recurrent HSV keratitis
    - Quiet
  - Iritis
    - Quiet
  - Cataract
    - Refer for cataract surgery went ready
    - Will increase Valtrex PO
  - Cataract surgery 1-18-2018
    - Increased Valtrex pre and post op
    - VA: OD 20/25

73-year-old white man

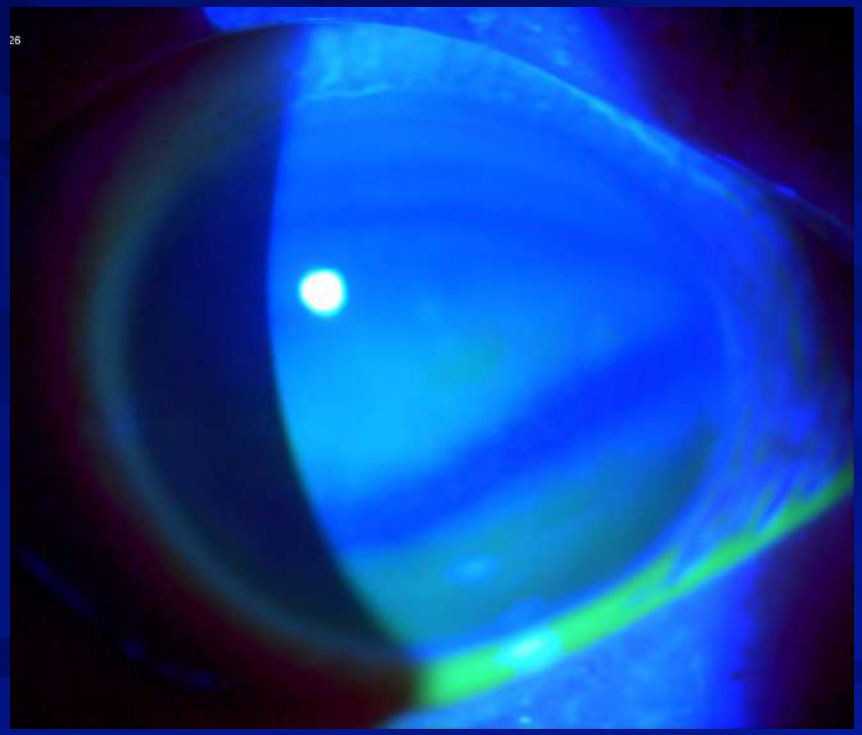


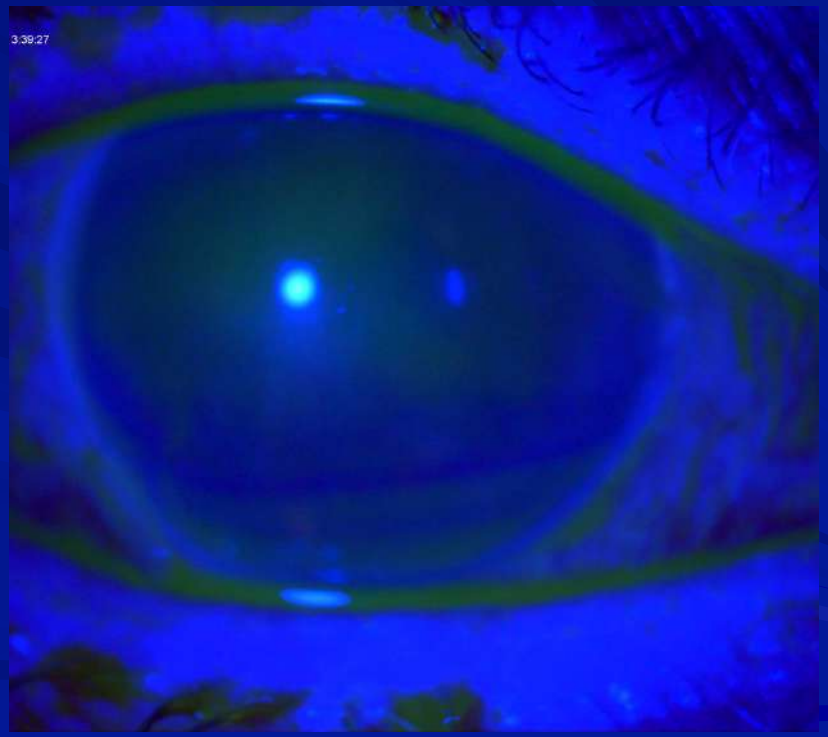


73-year-old white man



73-year-old white man





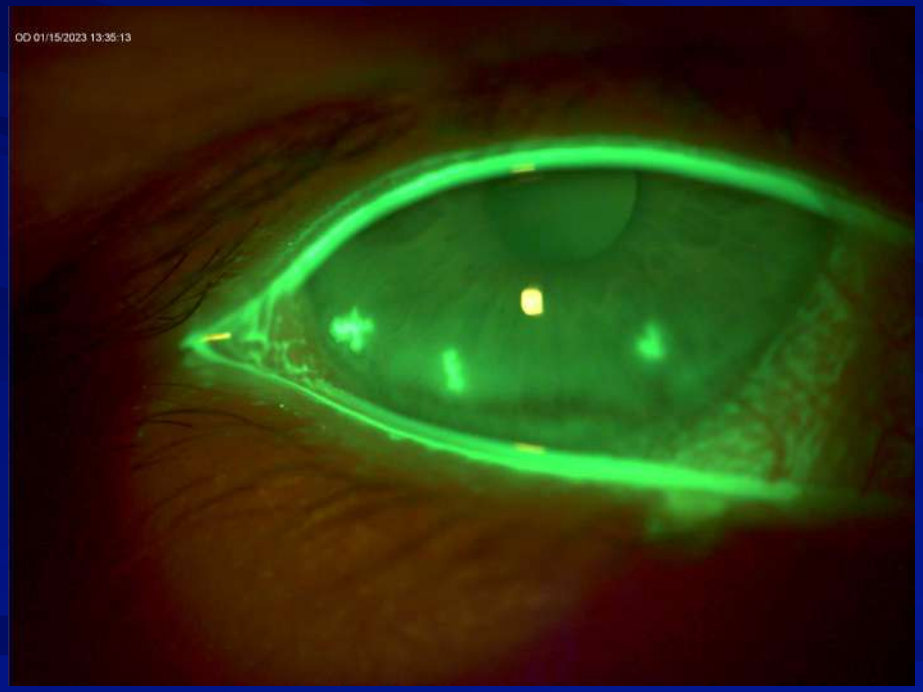
54-year-old white woman

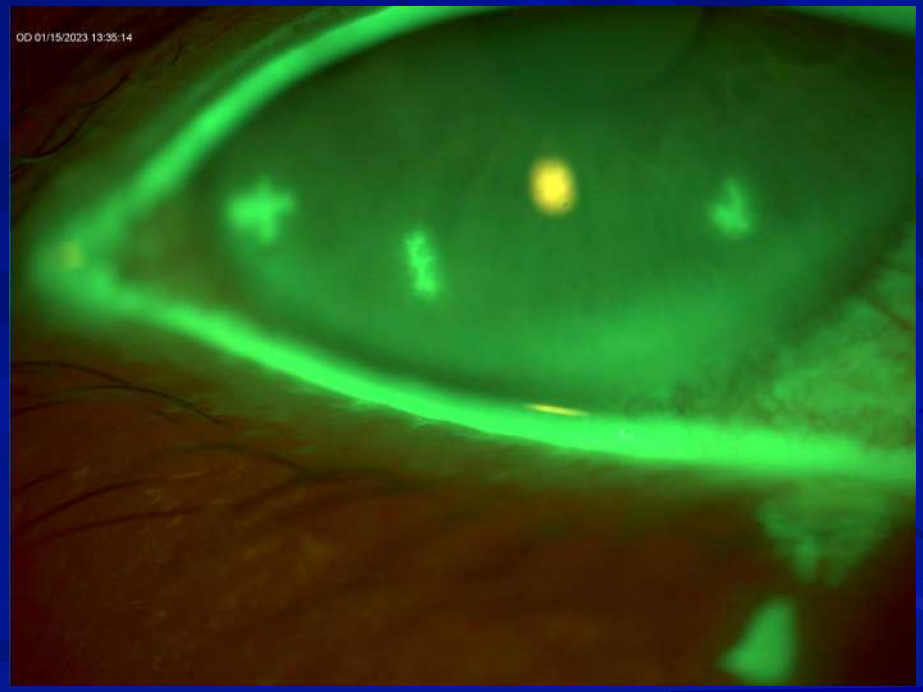
- Review of records of ECP: 12-30-2021 OD red, itch, - especially the inner corner
- PCP – ciprofloxacin 2 drops every 4 hours
  - Used for 2 days, no improvement
- Hurts into cheekbone

- Dx: cornea abrasion
- Tx: Maxitrol OD TID, check 1 week

- January 3, 2022 – patient wants 3rd opinion
- Eye started to improve over weekend, now redness and irritation is back
  - Not as itchy
  - Pressure when closes eyes

54-year-old white woman





Herpes Viruses are Classified by Their Location in the Latent State
Saw HSV cases now let's see Zoster

Human herpes type	Name	Sub Family	Target cell type	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Alphaherpesvirinae	Mucoepithelia	Neuron	Close contact usually sexual
3	Varicella Zoster virus (VSV)	Alphaherpesvirinae	Mucoepithelia	Neuron	Contact or respiratory route
4	Epstein-Barr Virus (EBV)	Gammaherpesvirinae	B lymphocyte, epithelia	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes and possibly others	Contact, blood transfusions, transplantation, congenital
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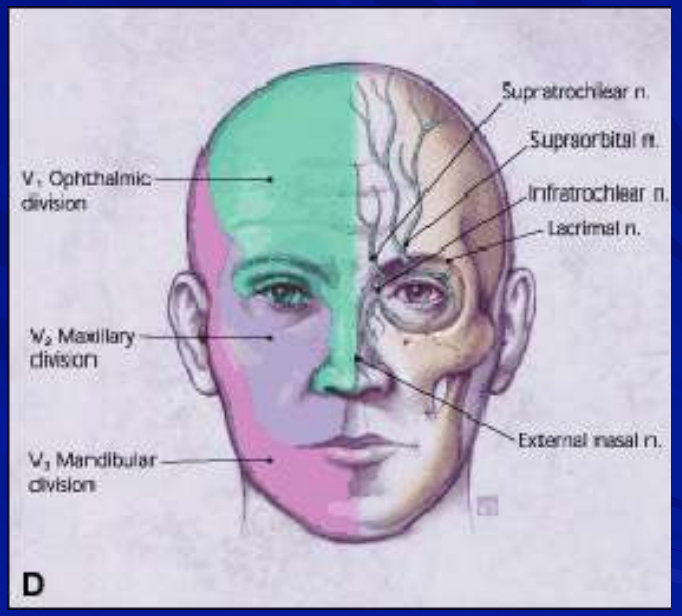
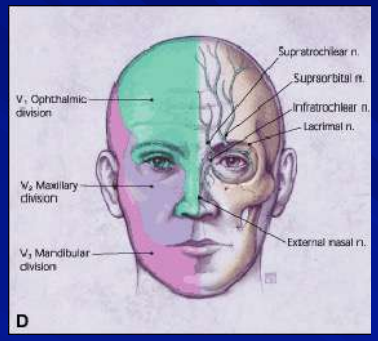
7	Human herpes virus-7 (HHV-7)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma-associated herpes virus (KSHV)	Gammaherpesvirinae	Endothelial cells	Unknown	Exchange of body fluids?

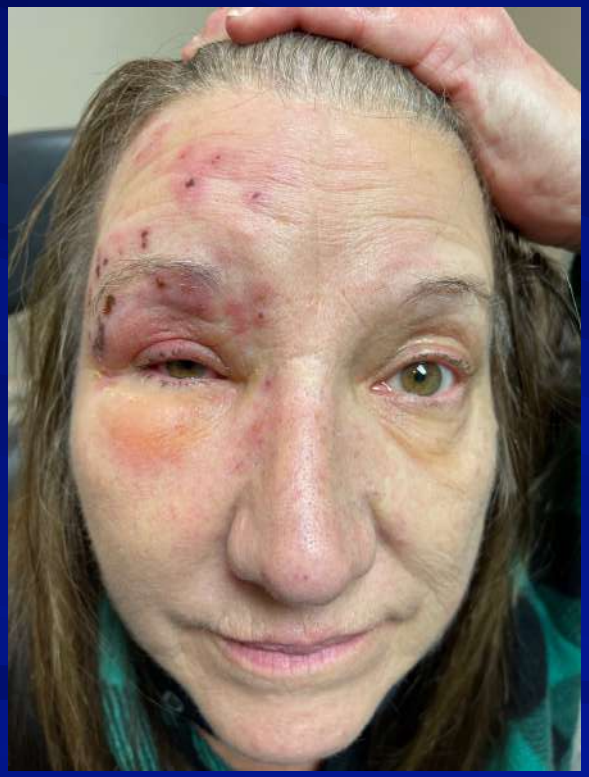


Varicella-Zoster Virus (VZV)

- AKA: Herpes Zoster Virus or Herpes Human Virus 3
- Vesicles on tip of nose indicate nasociliary involvement
  - High risk of ocular manifestations

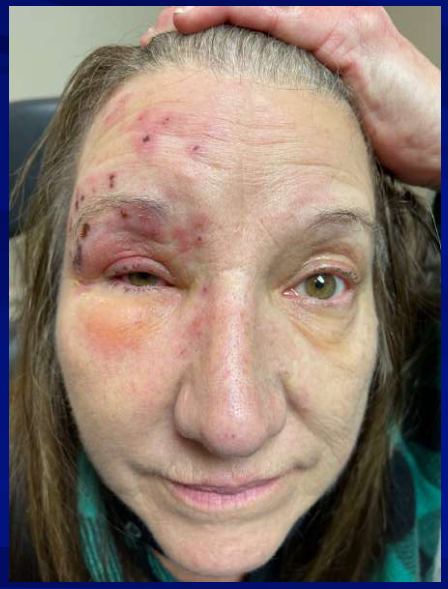


February 9, 2022



Zoster

February 9, 2022



February 16, 2022

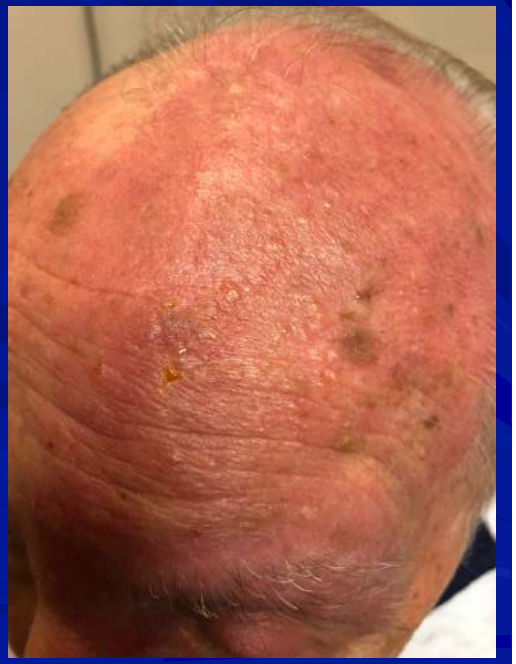
February 22, 2022

March 8, 2022

February 16, 2022

Zoster 9-16-2019



Zoster 9-23-2021

12-17-2021

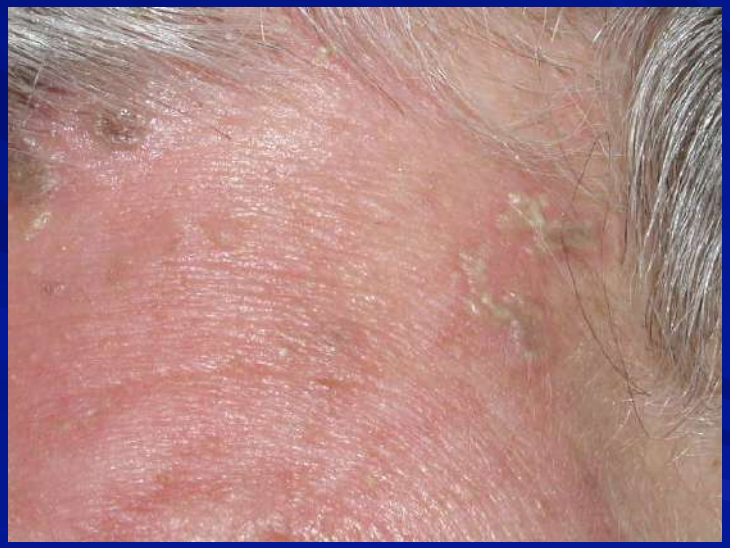
Valtrex


Valacyclovir Hcl
1Gm Tab Nort
NDC:16714-0697-03
For > Valtrex 1 Gm Tab Gax
Qty:30
No Refills

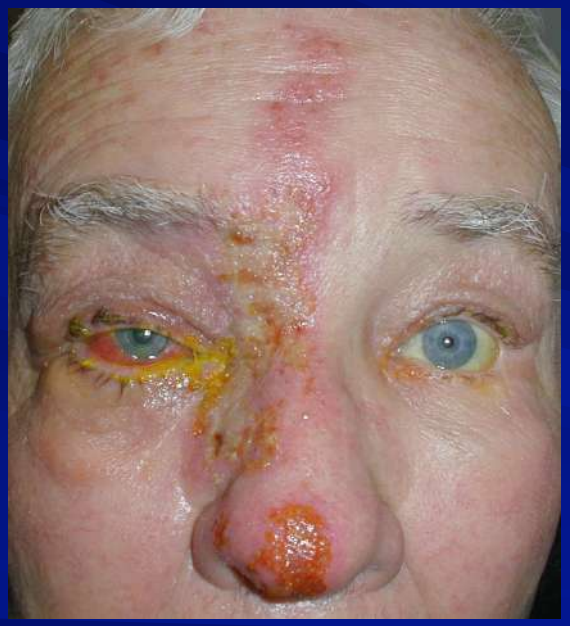
12-21-2021

Varicella-Zoster Virus (VZV)

- The best time to diagnose and treat



Varicella-Zoster Virus (VZV)



- Vesicles on tip of nose indicate nasocilliary nerve involvement
  - High risk of ocular manifestations
- Ocular findings associated with VZV
  - Episcleritis
  - Scleritis
  - Keratitis
  - Uveitis
  - Iris atrophy
  - Glaucoma
  - Vitritis
  - Retinitis
  - Choroiditis
  - Optic neuritis
  - CN palsy

24-48 hours before Zirgan arrives

- Zirgan
- Viroptic

- Orals only
- Orals and Amniotic Membrane

Herpes Simplex Virus Keratitis

- Infectious epithelial keratitis
- Stromal keratitis
- Endotheliitis
- Neurotrophic keratopathy

Bio Optix

Amniotic Extracellular Matrix

BioD

Allograft Tissue Information and Product Preparation Insert

Contents / How Supplied

This package contains Human Cellular and Tissue Based Products (HCT/P) as defined by US FDA 21 CFR Part 1271.

CAUTION:

Federal (USA) law restricts this product to sale by or on the order of a licensed physician.

The **Donated Human Tissue** has been determined eligible for transplantation by a licensed Medical Director according to the criteria listed in the Donor Selection section below.

Product Description

BioDOptix™ is a human amnion membrane allograft provided in prescribed geometric configurations. BioDOptix is dehydrated during processing and should be dry when the package is opened. The inner peel pouch and tissue product are terminally sterilized via E-beam irradiation and may be placed directly into the sterile field. Included in the packaging along with this insert are a Tracing Record and a set of patient labels.

- BioDOptix is sterilely packaged for single patient, one time use only.
- Once opened, BioDOptix must be used immediately or discarded.

Introduction

BioDlogics, LLC, is registered with the Food and Drug Administration (FDA) as a manufacturer and distributor of human cells, tissue, and cellular and tissue-based products (HCT/P). All donor recoveries are performed by BioRecovery, LLC, an affiliate of BioDlogics, LLC. BioRecovery, LLC is also registered with the FDA and adheres to the regulations regarding HCT/P recovery and the screening and testing of the tissue donor as verified through supplier audits.

Donor Selection

The Medical Director of the registered recovery agency has determined that the donor of the tissue contained in this product is eligible to donate tissue for transplantation based on meeting the following criteria:

1. **The results of donor screening indicated that the donor was free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases, and**
2. The results of donor testing for the following relevant communicable disease agents are negative or non reactive:
   - Antibodies to the human immunodeficiency virus type 1and type 2 (anti-HIV-1 and anti-HIV-2)
   - HIV-1/Hepatitis B/Hepatitis C by Transcription Mediated Amplification
   - Hepatitis B surface antigen (HBsAg)
   - Hepatitis B total core antibody
   - antibodies to the hepatitis C virus (anti-HCV)
   - Antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
   - Syphilis using FDA-licensed tests. If the blood sample to be used for syphilis screening is determined and documented to be unacceptable for the screening assay (e.g. hemolysis, sample testing time restriction) then an FDA-licensed treponemal-specific confirmatory assay may be performed instead (e.g. FTA-Abs).

All laboratories performing these tests are certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493 or have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS).

At the time of recovery, cultures of the tissue are taken and grown out for evaluation. Additionally, a donor's medical history and behavior risk assessment, incorporating U.S. Public Health Service guidelines, are obtained prior to donation. Discussions with physicians and/or the donor mother are conducted to identify circumstances that may lead to the exclusion of the donor or donated tissue. The blood sample test results, donor medical history, behavior risk assessment, physical assessment, and information from other sources or records, which may pertain to donor suitability, have been evaluated by a Medical Director. The Medical Director is a licensed physician who completes a comprehensive review of every donor record. The results are used to determine that the donor suitability criteria at the time of tissue recovery have been met, and that the tissue is acceptable for transplantation.

The names and addresses of the testing laboratories, the interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records and all pertinent donor medical information can be quickly retrieved upon request for any allograft tissue recovered on the behalf of BioDlogics, LLC.

Recovery

Tissue recovery is aseptically performed by BioRecovery, LLC, an FDA-registered tissue bank. At the time of recovery, medical records are collected and reviewed as part of donor eligibility.

Processing

BioDOptix is processed by BioDlogics, LLC, in a controlled environment using methods designed to prevent contamination and cross-contamination of the products. Technical quality assurance standards are rigorously maintained. Ethanol is used during processing and trace residuals remain on the product.

Tissue Distribution

BioDOptix is distributed by BioDlogics, LLC.

Tissue Storage

It is the responsibility of the Tissue Dispensing Service and/or end user to maintain BioDOptix in its original packaging and at room temperature until ready for use.

HCT/P Tracking

Important notice to end-user: Recipient records must be maintained for the purpose of tracing tissue post-transplant per The Joint Commission and FDA requirements. The allograft ID number must be recorded in the operative record. The Tracing Record must be completed and returned to BioDlogics, LLC. Patient labels which include tissue numbers are contained in this package to aid in the tracking process.

General Usage

~~BioDOptix is intended for use as a wound covering.~~ This product is an allograft tissue intended for homologous use at the direction of a physician.

Precautions

1. BioDOptix contains trace amounts of ethanol. It should not be used in patients with known sensitivity to ethanol.
2. In order to reduce the risk of complications, BioDOptix should not be in used the presence of active infection.
3. Although donor tissue is evaluated and processed following strict FDA guidelines, the donor screening methods are limited and may not detect all diseases. As with any allograft, complications at the graft site may occur post operatively that are not readily apparent. These include, but are not limited to:
   - transmission of communicable diseases, including those of unknown etiology
   - transmission of infectious agents such as viruses, bacteria and fungi
   - immune rejection of, or allergic reaction to, implanted HCT/P.

Adverse Reactions

Adverse reactions or outcomes that potentially involve the use of BioDOptix should be reported immediately to the BioDlogics, LLC Customer Service Department.

Recommended Instructions for use of BioDOptix

These recommendations are designed only to serve as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgment concerning patient care.

piece of sterile mesh to facilitate placement of the graft if the surgeon wants to hydrate the graft before application. The mesh reflects the epithelial side of the tissue (surface closest to the fetus).

Preparation Instructions

1. Open carton or box containing BioDOptix and remove the peel-pack.
2. Peel open the outer package and remove the inner foil pouch using aseptic technique.

Note:

-The inner tray and its contents are sterile and may be placed directly into the sterile field.

3. Peel the inner pouch open and place the implant with the accompanying mesh into the sterile field.

Note:

-Care must be taken in transferring/removing the graft from the package as it is lightweight and may be easily displaced.

-The BioOOptix graft is translucent and will look off-white or yellowish on the mesh that is still in contact with allograft.

-It is important to note that the drier the surface to be covered with the graft, the easier the application.

4. Remove the graft from the mesh and place it at the desired location.

If the allograft has been hydrated prior to application, leave the graft on the mesh to aid in placement.Once the graft is positioned in the desired location, grasp a corner of the allograft with forceps to hold it in place while gently peeling off the mesh.

DO NOT LEAVE ANY MESH IN WOUND

5. It is sometimes necessary to gently "brush" or "massage" the thin membrane at the edges to smooth out wrinkles and folds that can occur during graft placement.
6. If removal and replacement are needed, re-apply the mesh for ease of manipulation.
7. After final placement, discard the mesh.

Return Policy

All return orders of BioDOptix require a Return Authorization (RA) number before product may be returned for credit. Please contact the BioDlogics Customer Service Team for more information.

Note: BioDlogics LLC makes no claims concerning the biological properties of allograft tissues. All tissue has been collected, processed, stored, and distributed in compliance with the FDA regulations governing HCT/Ps. Although every effort has been made to ensure the safety of allograft material, current technologies may not preclude the transmission of disease.

General Usage

~~BioDOptix is intended for use as a wound covering.~~ This product is an allograft tissue intended for homologous use at the direction of a physician.

Precautions

1. BioDOptix contains trace amounts of ethanol. It should not be used in patients with known sensitivity to ethanol.
2. In order to reduce the risk of

complications, BioDOptix should not be in used the presence of active infection.

3. Although donor tissue is evaluated and processed following strict FDA

Cryopreserved

Indications:

- PROKERA is intended for use in eyes in which ocular surface cells are damaged or underlying stroma is inflamed or scarred. Acting as a self-retaining biologic corneal bandage, PROKERA effectively treats superficial corneal surface diseases by suppressing inflammation and related pain, promoting epithelial healing, and avoiding haze.
- PROKERA is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions. Placement of the conformer also enables application of the cryopreserved amniotic membrane to the ocular surface without the need for sutures.
- PROKERA is for single-use only in one patient by an ophthalmologist or optometrist.

Contraindications:

- PROKERA should not be used in eyes with glaucoma drainage devices or filtering bleb.

Precautions:

Location & Temperature	Use After Receipt
Unopened insulated shipping container	Within the expiration date printed on outer shipping box
-80°C → 4°C (-112°F → 39.2°F) Example: ultra-low temperature freezer, standard freezer, or standard refrigerator	Within the expiration date printed on product packaging (shelf-life is 2 years from date of manufacture)

37-year-old woman
OD red and painful

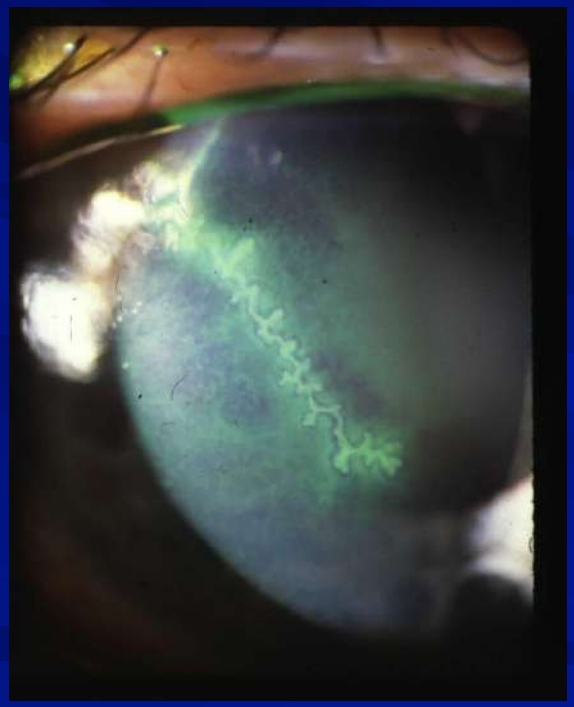
Va	20	30
cc		20

Current Correction
R -2.50-1.00 x 180
L -3.25-1.00 x 180

EOMS: full, unrestricted
CT: ortho D/N

PERRL (-)APD
CF: full by FC OU

Slit Lamp Evaluation

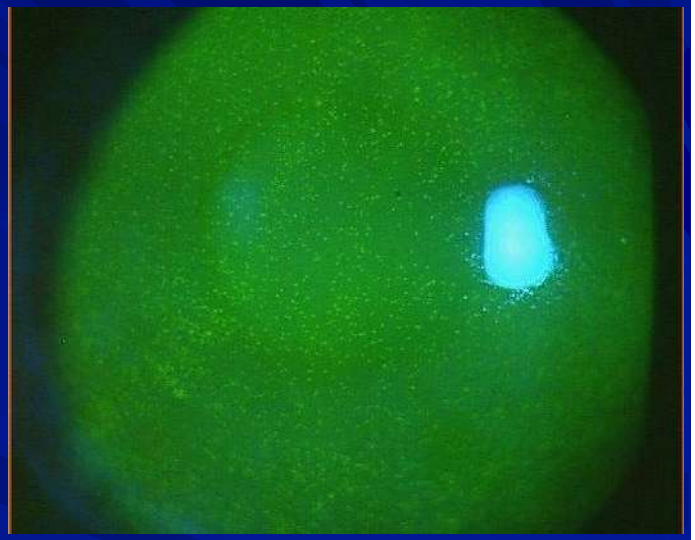


- Diagnosis
- Ocular history
  - First episode
- Treatment
- Maintenance of oral antiviral?

4 weeks later

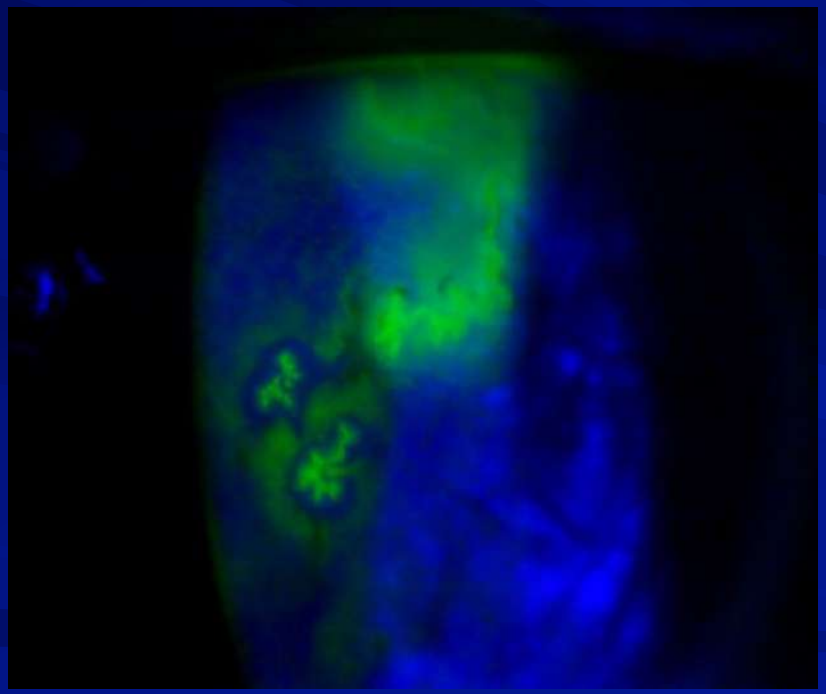
- Resolved
- Chance of occurring again within 12 months?
  - 25%

Cranium Keeper



- Viroptic (trifluridine solution) should be used for how long?
  - One drop every 2 hours while awake (up to 9 drops per day)
  - 21 days via package insert/instructions
- Zirgan (ganciclovir ophthalmic gel) 0.15%
  - One drop five times per day until the corneal ulcer heals
  - Then one drop three times per day for seven days

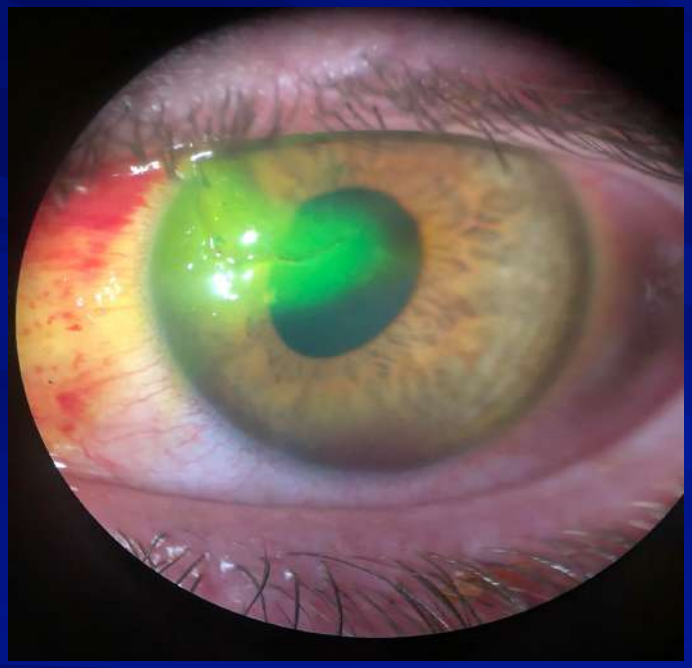
Slit Lamp Evaluation

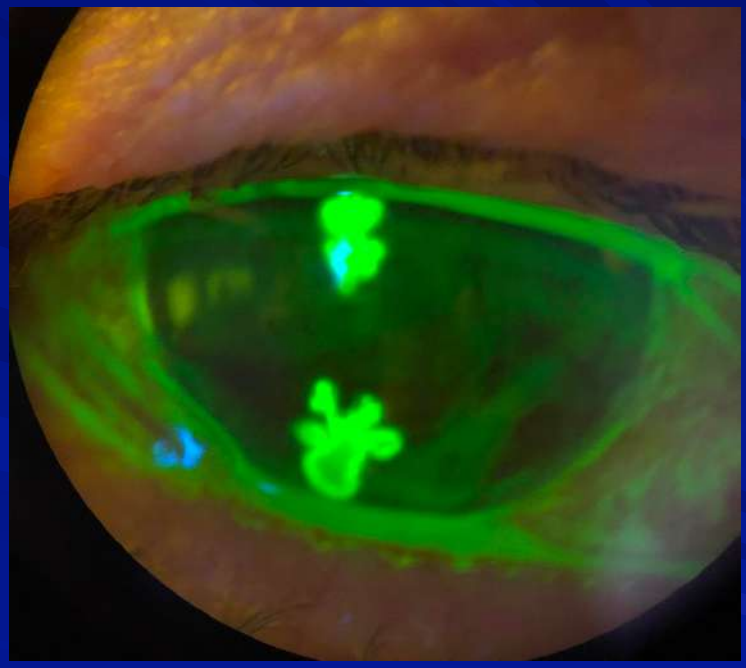


- 5 months later
- Treatment
- Maintenance of oral antiviral?
  - Education patient on treatment options
    - 43% occurring again

4 Months Later

- Ocular history
  - Third episode
- Treatment
- Oral antiviral maintenance?
  - What dosage?
    - Short term
    - Long term





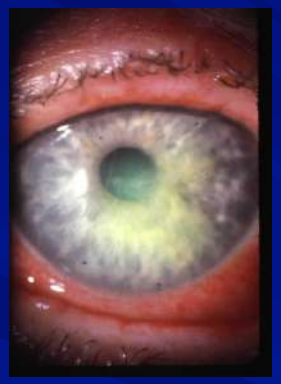
Herpetic Eye Disease Study

- HEDS I
  - Benefit from steroids in stromal keratitis
  - No benefit from oral Acyclovir in stromal keratitis
  - Benefit from steroids if iritis present

HEDS II

- No benefit from Acyclovir to stop progression to stromal or iridocyclitis
- Maintenance dose 400 mg BID, decreases recurrence by 41% within 1st year

Recurrent Herpes Simplex Keratitis



- Treatment
  - ★ Topical antiviral
  - ★ Oral antiviral
- Remember to check for?
- Patient is allergic to Penicillin and Keflex
- Patient is also 2 months pregnant

Medical History

- Before we Rx any medications we take a thorough *medical* history which includes:
  - CC
  - HPI
  - ROS
    - Kidney disease, liver disease, dialysis
  - PFS History
  - Current Medications
  - Allergies…Adverse Reactions/Allergies
  - Pregnancy…any chance you might be pregnant?

FDA Pregnancy Categories

- Category A- studies in pregnant women…no risk
- Category B- animal studies no risk but human not adequate…or…animal toxicity but human studies no risk…safe
- Category C- animal studies show toxicity human studies inadequate but benefit of use may exceed risk…OR…there are no adequate studies in animals or humans…avoid (MOST new drugs are here)
- Category D- evidence of human risk but benefits may outweigh risks…avoid
- Category X- fetal abnormalities, risk>benefits…avoid

Pregnancy and Lactation Labeling Rule-FDA

December 4, 2014 Final Rule

- **Effective June 30, 2015**
  - Effective now for new medications and a 3-5 year phase in period (application)
- Labeling for human prescription drugs and biological products will include:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
- Pregnancy (8.1)
  - Pregnancy Exposure Registry – omit if not applicable
  - Risk Summary – required subheading
  - Clinical Considerations- omit if none of the headings are applicable
    - Disease-associated maternal and/or embryo/fetal risk- omit if not applicable
    - Dose adjustments during pregnancy and the postpartum period - omit if not applicable
    - Maternal adverse reactions - omit if not applicable
    - Fetal/Neonatal adverse reactions- omit if not applicable
    - Labor or delivery - omit if not applicable
  - Data- omit if none of the headings are applicable
    - Human Data - omit if not applicable
    - Animal Data- omit if not applicable

Pregnancy and Lactation Labeling Rule-FDA

December 4, 2014 Final Rule

- Lactation (8.2)
  - Risk Summary- required subheading
  - Clinical Considerations– omit if not applicable
  - Data– omit if not applicable
- Females and Males of Reproductive Potential (8.3) - omit if none of the headings are applicable
  - Pregnancy testing– omit if not applicable
  - Contraception– omit if not applicable
  - Infertility – omit if not applicable

Pre-June 30, 2015

respectively, revealed no evidence of teratogenicity.

8.3 Nursing Mothers

Following oral administration of a 500 mg dose of VALTREX to 5 nursing mothers, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500 mg maternal dosage of VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day. This would result in less than 2% of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. Caution should be exercised when VALTREX is administered to a nursing woman.

8.4 Pediatric Use

VALTREX is indicated for treatment of cold sores in pediatric patients ≥12 years of age and for treatment of chickenpox in pediatric patients 2 to <18 years of age *[see Indications and Usage (1.2), Dosage and Administration (2.2)]*.

The use of VALTREX for treatment of cold sores is based on 2 double-blind, placebo-controlled clinical trials in healthy adults and adolescents (≥12 years of age) with a history of recurrent cold sores *[see Clinical Studies (14.1)]*.

The use of VALTREX for treatment of chickenpox in pediatric patients 2 to <18 years of age is based on single-dose pharmacokinetic and multiple-dose safety data from an open-label trial with valacyclovir and supported by efficacy and safety data from 3 randomized, double-blind, placebo-controlled trials evaluating oral acyclovir in pediatric patients with chickenpox *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

The efficacy and safety of valacyclovir have not been established in pediatric patients:

- <12 years of age with cold sores
- <18 years of age with genital herpes
- <18 years of age with herpes zoster
- <2 years of age with chickenpox
- for suppressive therapy following neonatal HSV infection.

The pharmacokinetic profile and safety of valacyclovir oral suspension in children <12 years of age were studied in 3 open-label studies. No efficacy evaluations were conducted in any of the 3 studies.

Study 1 was a single-dose pharmacokinetic, multiple-dose safety study in 27 pediatric patients 1 to <12 years of age with clinically suspected varicella-zoster virus (VZV) infection *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

Study 2 was a single-dose pharmacokinetic and safety study in pediatric patients 1 month to <6 years of age who had an active herpes virus infection or who were at risk for herpes virus infection. Fifty-seven subjects were enrolled and received a single dose of 25 mg/kg valacyclovir

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of VALTREX. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to VALTREX.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria *[see Contraindications (4)]*.

CNS Symptoms: Aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, dysarthria, encephalopathy, mania, and psychosis, including auditory and visual hallucinations, seizures, tremors *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), (8.6)]*.

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Renal failure, renal pain (may be associated with renal failure) *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), (8.6)]*.

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS *[see Warnings and Precautions (5.1)]*.

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

7 DRUG INTERACTIONS

No clinically significant drug-drug or drug-food interactions with VALTREX are known *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

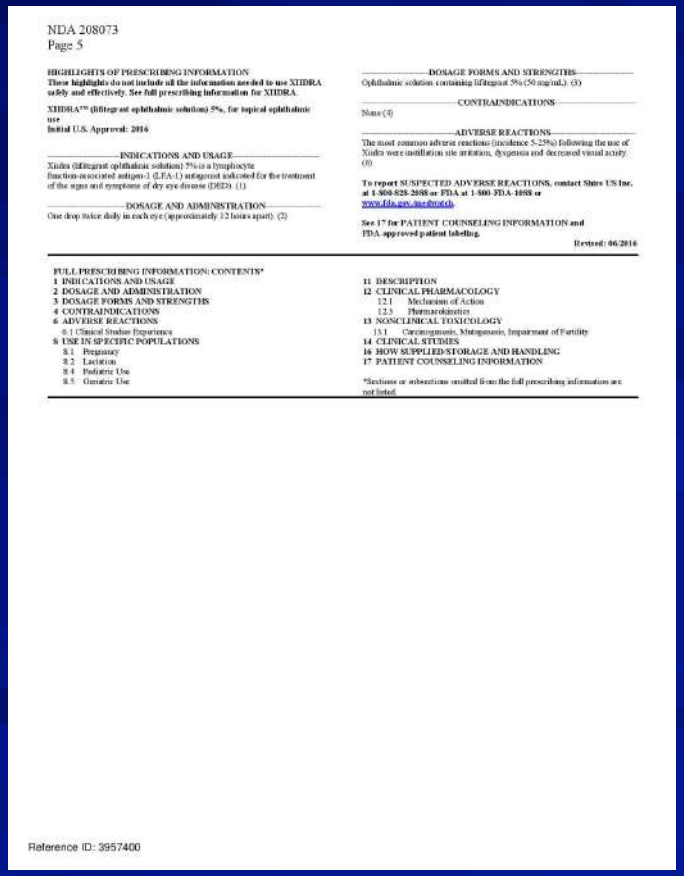
8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of VALTREX or acyclovir in pregnant women. Based on prospective pregnancy registry data on 749 pregnancies, the overall rate of birth defects in infants exposed to acyclovir in-utero appears similar to the rate for infants in the general population. VALTREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.

Animal reproduction studies performed at oral doses that provided up to 10 and 7 times the human plasma levels during the period of major organogenesis in rats and rabbits,

Post-June 30, 2015



NDA 208073
Page 5

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA™ (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

DOSAGE AND ADMINISTRATION
One drop twice daily in each eye (approximately 12 hours apart). (2)

DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing lifitegrast 5% (50 mg/mL). (3)

CONTRAINDICATIONS
None (4)

ADVERSE REACTIONS
The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

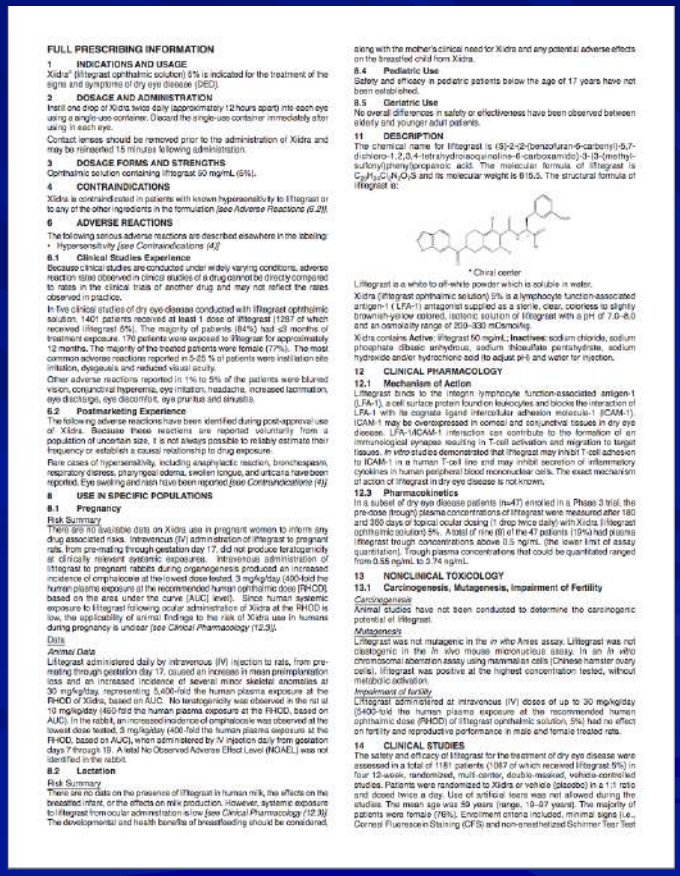
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3957400



FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

2 DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

3 DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing lifitegrast 50 mg/mL (5%).

4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:
- *Hypersensitivity [see Contraindications (4)]*

6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received **at least** 1 dose of **lifitegrast** (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 176 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity.

Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3)]*.

Data
Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (900-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION
The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propionic acid. The molecular formula of lifitegrast is $C_{29}H_{22}Cl_2N_2O_7S$ and its molecular weight is 615.5. The structural formula of lifitegrast is:

* Chiral center

Lifitegrast is a white to off-white powder which is soluble in water.

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist supplied as a sterile, clear, colorless to slightly brownish-yellow colored, isotonic solution of lifitegrast with a pH of 7.0–8.0 and an osmolality range of 260–330 mOsmol/kg.

Xiidra contains **Active:** lifitegrast 50 mg/mL; **Inactives:** sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in dry eye disease. LFA-ICAM-1 interaction can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies demonstrated that lifitegrast may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. The exact mechanism of action of lifitegrast in dry eye disease is not known.

12.3 Pharmacokinetics
In a subset of dry eye disease patients (n=47) enrolled in a Phase 3 trial, the pre-dose (trough) plasma concentrations of lifitegrast were measured after 180 and 360 days of topical ocular dosing (1 drop twice daily) with Xiidra (lifitegrast ophthalmic solution) 5%. A total of nine (9) of the 47 patients (19%) had plasma lifitegrast trough concentrations above 0.5 ng/mL (the lower limit of assay quantitation). Trough plasma concentrations that could be quantitated ranged from 0.55 ng/mL to 3.74 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis
Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility
Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

14 CLINICAL STUDIES
The safety and efficacy of lifitegrast for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to Xiidra or vehicle (placebo) in a 1:1 ratio and dosed twice a day. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 19–97 years). The majority of patients were female (76%). Enrollment criteria included, minimal signs (i.e., Corneal Fluorescein Staining (CFS)) and non-anesthetized Schirmer Tear Test

Renal Impairment

- Identify patients on hemodialysis
- Adjustment made by patient's creatinine clearance (CrCl)…ml/min
  - ★Work with patient's PCP/Internist

Oral Anti-Virals

- 3rd generation, go into every cell but only activate in viral infected cells
  - (1st generation=mutagenic)

- Use prophylactically prior to PKP, LASIK and PTK

Zovirax (acyclovir)

- Good for simplex and zoster
- Available in 200, 400 and 800 mg, IV
- Dosage: 800 mg/5 times/day (4 grams daily)
  - Poor GI absorption
- Maintenance dose: 200-400 mg bid
- Caution if impaired renal function
  - Excreted by kidneys
- Category B

Off-Label

- Valtrex and Famvir used for the eye
  - Off label
  - Only approved for genital herpes
  - Won't find dosage in PDR for ocular usage

Famvir (famciclovir)

- Available in 125, 250 and 500 mg
- Dosage: Zoster 500 mg tid
  Recurrent Simplex 125-250 mg bid
- Caution if impaired renal function
- Category B

- No longer available via Norvartis in USA as brand name

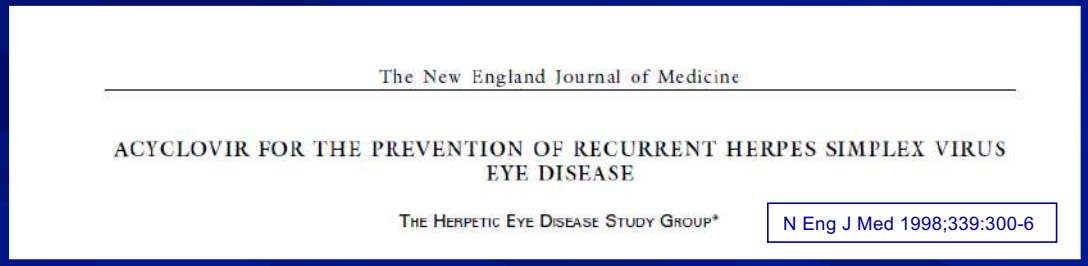
Valtrex (valacyclovir)

- Pro-drug of acyclovir
- Available in 500 and 1000 mg
- GI upset
- HSV-1, HSV-2, VZV
- Dosage: 1g tid x 1 week (3 grams daily)
- Caution if impaired renal function
- Category B

- Treatment
  - Zirgan 0.15%
    - Caution Zirgan and Viroptic are Category C
  - Steroid
  - Artificial tears
  - Valtrex
    - 1000 mg TID PO
    - 500 mg QD PO
  - Add/consider L-Lysine

Beside the dosing frequencies…

- What is different about the oral antivirals?



The New England Journal of Medicine

ACYCLOVIR FOR THE PREVENTION OF RECURRENT HERPES SIMPLEX VIRUS EYE DISEASE

THE HERPETIC EYE DISEASE STUDY GROUP*

N Eng J Med 1998;339:300-6

- Main reason for early discontinuation of oral acyclovir in HEDS
  - Gastrointestinal side effects
  - Rash

Many patients on oral acyclovir have GI symptoms

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Acyclovir

Zovirax® contains lactose

Presence or absence of lactose in generic acyclovir varies

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of the antiviral drug acyclovir.

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Valacyclovir

Valtrex® and all generics are free of lactose

FAMVIR tablets contain 125 mg, 250 mg, or 500 mg of famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

Generics available in the US contain lactose

* In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

CNS Effects in Elderly Patients

- Acyclovir and valacyclovir carry a higher risk of CNS adverse effects in the elderly:
  - Agitation
  - Hallucinations
  - Confusion
- Clinical Take Home Point:
- Consider famciclovir in older patients who CNS side effects with acyclovir or valacyclovir
- Other major concern with elderly patients is age-related reduced kidney function

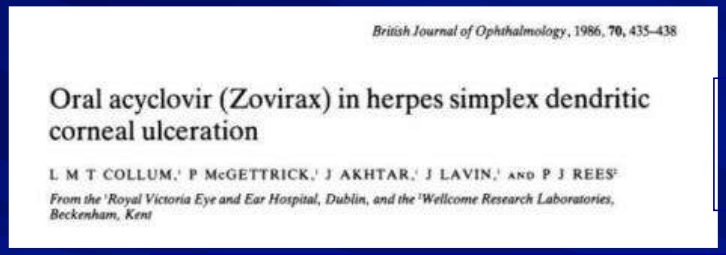
Is there a difference in efficacy between topical and orals in the various forms of ocular herpes?

Ganciclovir ophthalmic gel

Oral antivirals:

- Acyclovir
- Valacyclovir
- Famciclovir

The deeper the involvement, the more efficacious orals become.
But what about epithelial keratitis?...There seems to be equivalence



British Journal of Ophthalmology, 1986, **70**, 435–438

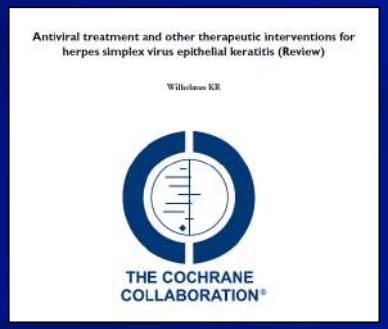
Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration

L M T COLLUM,[1] P McGETTRICK,[1] J AKHTAR,[1] J LAVIN,[1] AND P J REES[2]

From the [1]Royal Victoria Eye and Ear Hospital, Dublin, and the [2]Wellcome Research Laboratories, Beckenham, Kent

60 patients with HSV dendritic ulceration included a small number with stromal involvement keratitis randomized to oral vs. topical acyclovir

No statistically significant difference in to time to resolution (mean = 5 days)



Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis (Review)

Wilhelmus KR

THE COCHRANE COLLABORATION®

"Oral acyclovir alone appeared as effective as topical antiviral therapy in the treatment of simplex epithelial keratitis."

Oral delivery appears to get to corneal target even though it is an avascular tissue!

Cochrane Database Syst Rev 2010:8(12):1-198.

Lysine or L-Lysine

- An essential amino acid
- It is necessary for human health

- But the body can't manufacture it

- You have to get lysine from food or supplements
- Amino acids like lysine are the building blocks of protein
  - Lysine is important for proper growth

Lysine and Herpes

- Some studies have found that taking lysine on a regular basis may help prevent outbreaks of cold sores and genital herpes
- Lysine has antiviral effects by blocking the activity or arginine
  - Which promotes HSV replication
- One review found that oral lysine is more effective for preventing an HSV outbreak than it is at reducing the severity and duration of an outbreak
- One study found that taking lysine at the beginning of a herpes outbreak did not reduce symptoms.

- Typically comes in 500 mg
  - 2000-3000 mg while active or infectious
  - 1000 mg as maintenance

Cranium Keeper

- Percentages in HSV keratitis
  - 25%
  - 43%
  - 41%

Vaccines

- Zostavax™ – live vaccine; 60 years and older
  - "the only game in town…"
    - 50-ish% effective; 1 dose
    - Efficacy wanes after 4-5 years
- Shingrix™ – has replaced Zostavax™
  - We are moving in the right direction!
  - Recommended for 50 years and older
    - 90+% effective?; 2 doses; IM; recombinant vaccine
    - Efficacy *seems* solid up to 7-8 years

Prevention Through Vaccination

- How effective are today's vaccines?

- Zostavax (Merck)- subcutaneous injection
  - Does not confer life-long immunity … effect wanes after 5 years with booster suggested at 10 years
  - 38-70% reduction in risk of shingles after vaccination
  - 60-70% reduction in occurrence of PHN
  - Not recommended for patients with post-HZV corneal or intraocular infection
  - Patients with previous shingles may experience ocular, dermatologic, or disseminated disease

- Shingrix- Subunit Vaccine HZ/su (GSK)- intramuscular 2 injections
  - Recombinant VZV glycoprotein E with AS01B adjuvant system
  - Primary vaccine with second dose 2 months later
  - ZOE-50 trial reduced risk of shingles by 97% (Cunningham, etal NEJM 2016)
  - ZOE-70 trial reduced risk of shingles by 90% (Cunningham, etal NEJM 2016)
  - Pooled data demonstrated HZ/su associated risk reduction of PHN by 89%
  - Potentially beneficial for immunocompromised individuals

Serious Complications of Herpetic Eye Disease

- Neurotrophic States
- Acute Retinal Necrosis
- Post Herpetic Neuralgia

Post Herpetic Neuralgia

How To Treat and Possibly Avoid It

Post Herpetic Neuralgia (PHN)

- Patients with PHN report decreased quality of life and interference with activities of daily living
- Approximately 1 million cases of herpes zoster occur annually in the US
  - One in every three people develops herpes zoster during their lifetime
- PHN is a frequent complication occurring in 5% to 15% of cases
  - Causing moderate to severe neuropathic pain
- PHN is a neuropathic pain syndrome characterized by pain that persists for months to years after resolution of the herpes zoster rash
- Neuropathic pain
  - Does not respond consistently to classic non-opioid analgesic drugs
  - Better treated with antidepressant, anticonvulsant drugs and topical agents
- Neuropathic pain is a major public health problem worldwide
  - Unclear mechanism
  - Treatment is one of the most difficult medical problems

Post Herpetic Neuralgia (PHN) Treatment

- Approaches to management of post herpetic neuralgia include
  - Preventing herpes zoster through vaccination and/or antiviral treatment
  - Administering specific medications to treat pain

- First-line drugs
  - Anti-convulsant -neuropathic pain
    - Calcium channel α2-δ ligands
    - gabapentin (Neurontin) and pregabalin (Lyrica)
  - Tricyclic antidepressants
    - amitriptyline, nortriptyline, desipramine
  - Topical lidocaine patches
    - Works because PHN is a peripheral neuropathy
    - **Radicular pain** is a type of **pain** that radiates into the lower extremity directly along the course of a spinal nerve root (topical lidocaine not effective)

Lyrica - pregabalin
Neurontin - gabapentin

- Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin?
  - Patients with chronic pain conditions such as neuropathic pain frequently experience delays in diagnosis and treatment
  - Pregabalin significantly improves pain irrespective of the length of time since onset of neuropathic pain

Pain Pract. 2016 Sep 2. doi: 10.1111/papr.12469. **Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin?** Pérez C[1], Latymer M[2], Almas M[3], Ortiz M[3], Clair A[3], Parsons B[3], Varvara R[2].

Neurotropic Cornea Ulcer

- Difficult to manage due to:
  - Decreased ocular innervation
  - Decreased tears production
- Medications to avoid
  - Topical corticosteroids
    - May increase collagenase activity and promote stromal melting
  - Topical NSAIDs
    - No shown benefit in wound healing
    - Can decrease corneal sensitivity

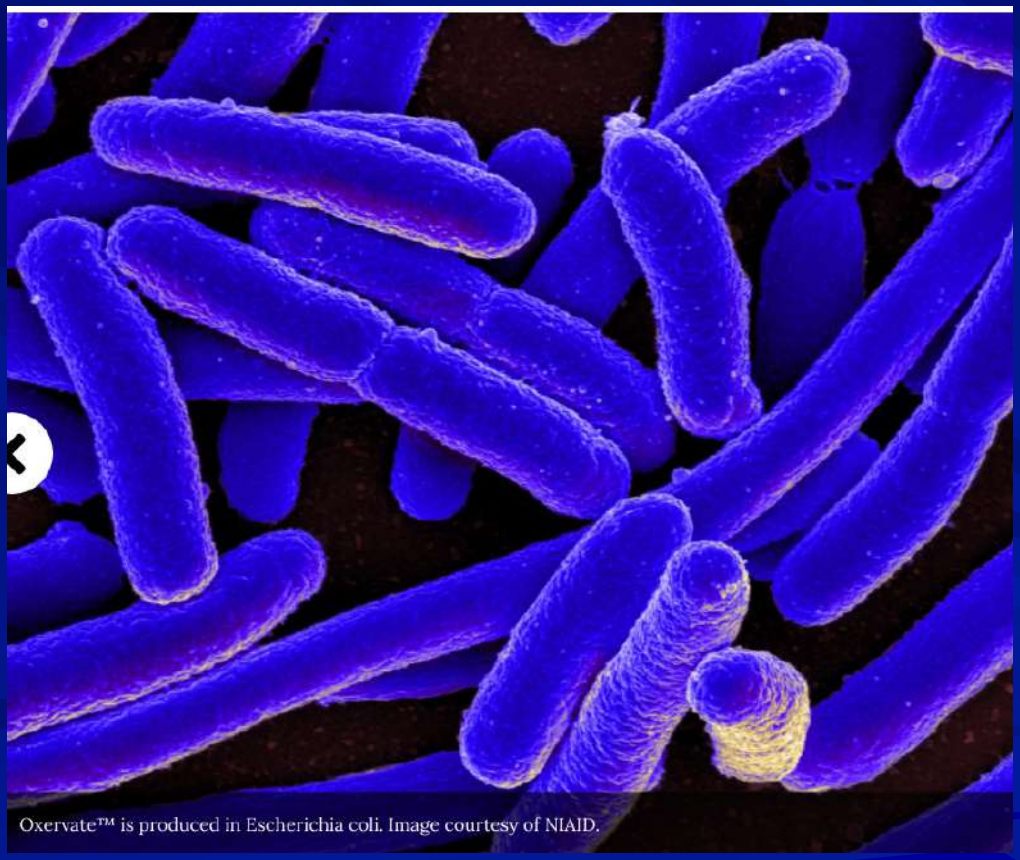
Neurotropic Cornea Ulcer

- Traditional Treatments
  - Preservative-free artificial tears, gels, and ointments
  - Discontinuation of any topical ocular therapies
    - Those that can decrease corneal sensitivity
      - timolol, betaxolol, sulfacetamide, diclofenac, ketorolac
    - Those that contain preservatives
  - Punctal occlusion
  - Doxycycline 100 mg PO qd/qod; anti-inflammatory properties
  - Autologous blood serum
- Alternative to traditional treatments
  - Scleral contact lenses
  - Amniotic Membrane

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

Escherichia Coli



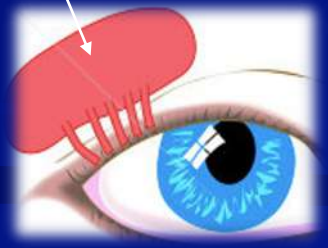
Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Corneal Homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

Corneal nerves stimulate blinking and tear production

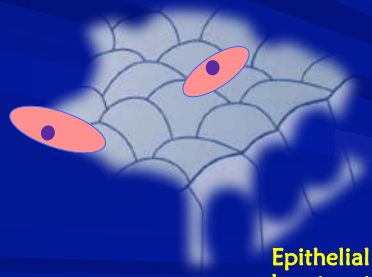
Tear gland



Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation



Epithelial cells and keratocytes

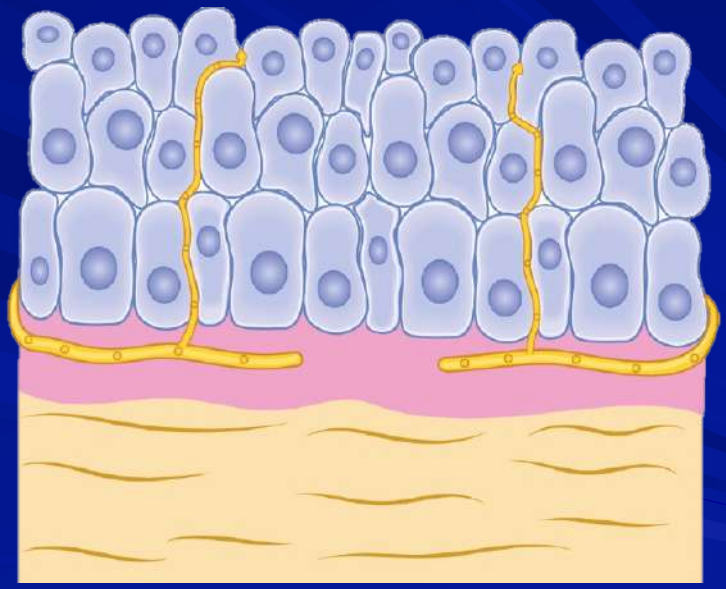
Neuromediators provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

- Stimulates wound healing
- Maintains anatomic integrity

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

Pathophysiology of NK[1]

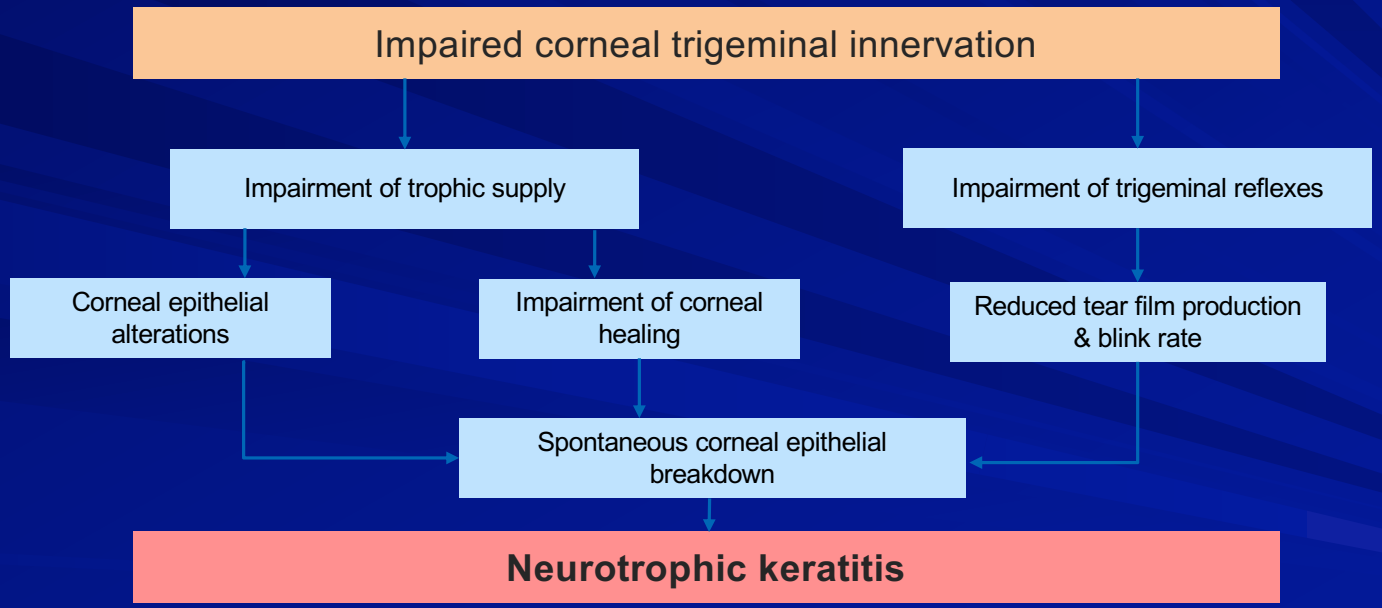
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production 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.

Trigeminal nerve damage leading to NK[1]



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

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

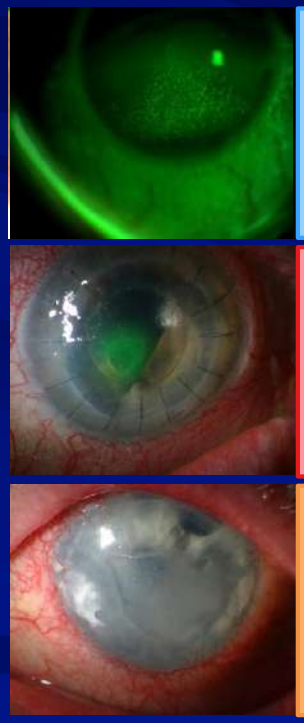
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

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.

NK classification



Images by kind consent of Prof. Messmer and Prof. Dua

Stage 1: 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 2: Moderate

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

Stage 3: Severe

(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. Semarero F, et al. Ophthalmologica 2014;231:191-7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

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.

Corneal Sensitivity

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]

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

TEAR SECRETION

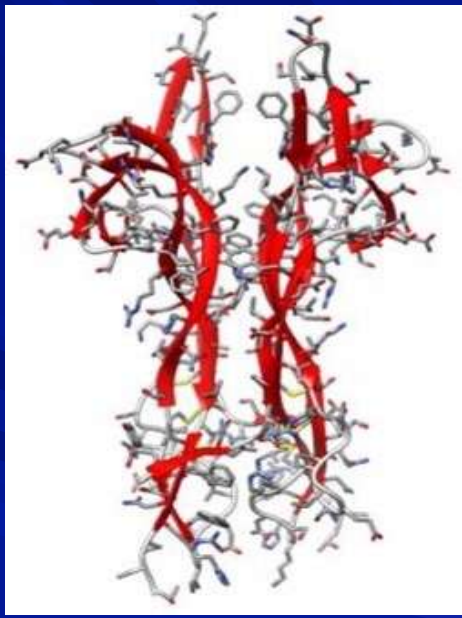
CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

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. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1163–1168

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.

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

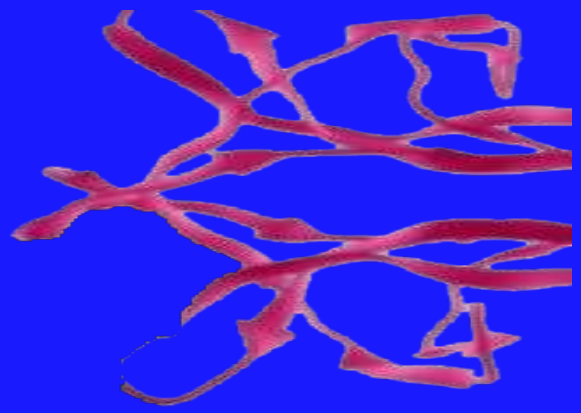
The Delivery System Kit Contains:

- 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

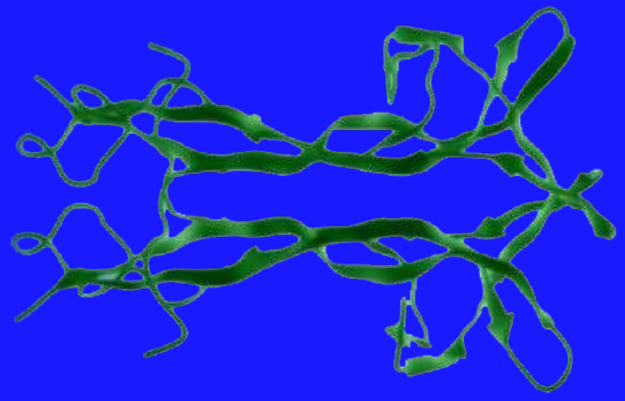
- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

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

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues



Cenegermin



Endogenous NGF

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.

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)

Every 2 hours

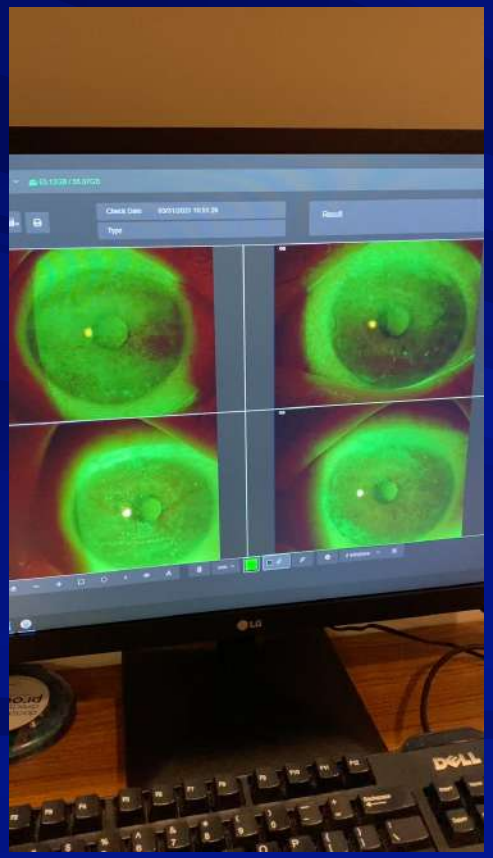
Apply 6 times daily

Continue for 8 weeks

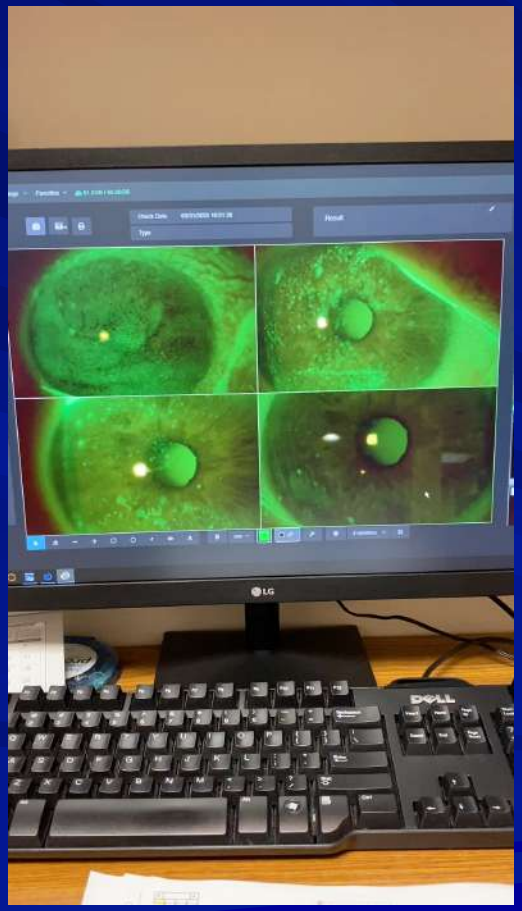
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Let's Hear From a Patient

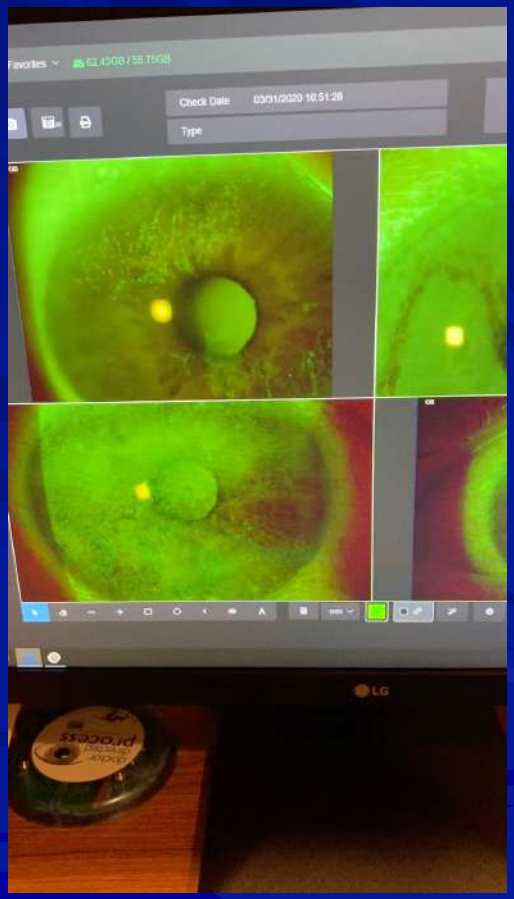
April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks



May 12, 2020 - After 6 weeks



Study Conclusions

After 8 weeks of treatment, 6 times daily

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

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.

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

European patients with NK in one eye

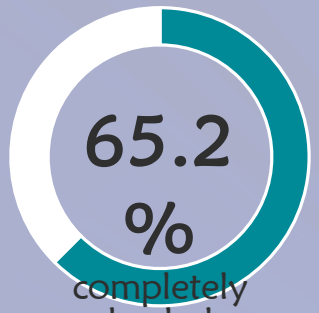
NCT01756456

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Vehicle response rate 16.7%

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[3]

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. BOC, R. 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.

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.

Oxervate™ (cenegermin-bkbj)

- Approved 2018
- Dompé farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis

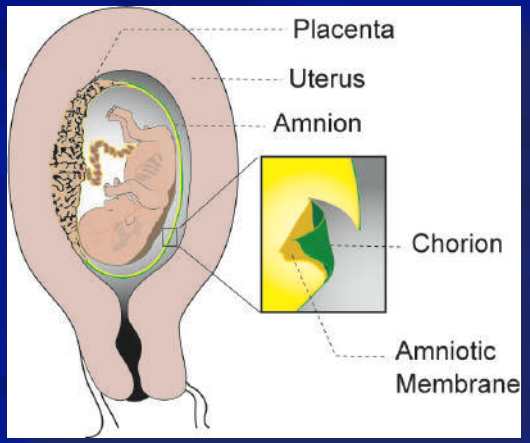
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2 hour intervals) for 8 weeks

- 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

Sutureless Amniotic Membrane

- Amniotic membrane is the innermost lining of the placenta (amnion)
  - Shares the same cell origin as the fetus
  - Stem Cell behavior
- Regenerative platform that possesses natural growth factors and scaffolding properties that are
  - Anti-inflammatory
  - Anti-scarring
  - Anti-angiogenic
- **Therapeutic action**
  - Promotes Stem Cell Expansion
  - Suppresses pain
  - Promotes cellular migration
  - Expedites recovery



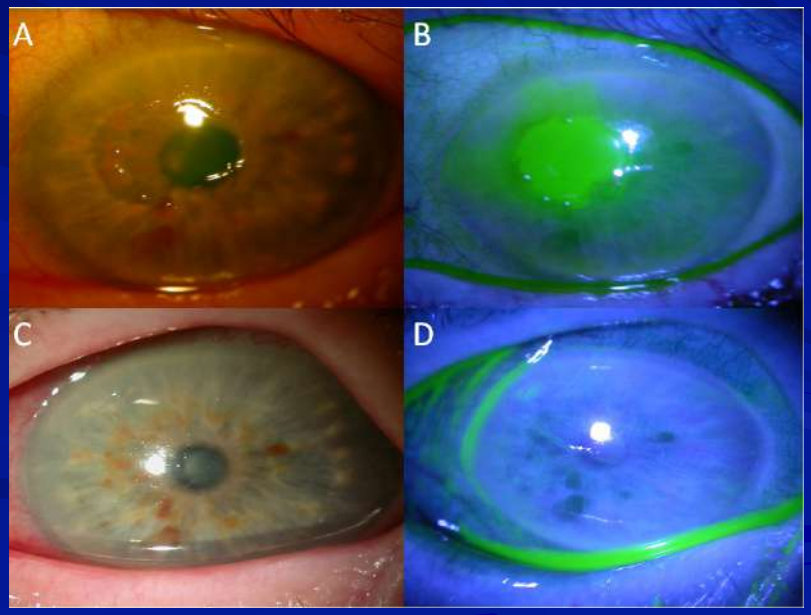
Cryopreserved and Dehydrated

- Cryopreserved
  - PROKERA- Biotissue
- Dehydrated
  - AmbioDisk -IOP Ophthalmics
  - BioDOptix – BioD
- Taped tarsorrhaphy/tapesorrhaphy

67-year-old woman with a history of recurrent HSV keratitis and dry eye

- She presented with mild ocular discomfort (cornea hypoesthesia) and progressive decrease of vision (20/400) for several weeks
- Examination revealed a central corneal epithelial defect surrounded by a rim of loose epithelium, stromal edema, and anterior chamber inflammatory reaction (Fig. A, B)
- Neurotrophic keratitis

- PROKERA® was placed along with punctal plug, tapesorrhaphy, and oral Acyclovir
- Complete healing occurred within one week, resulting in clear cornea, 20/20 vision, and improved tear meniscus (Fig. C, D).



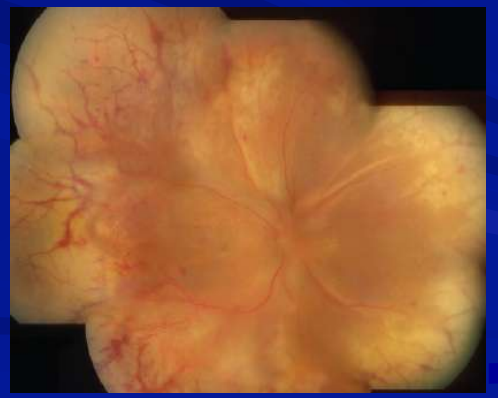
Early intervention with PROKERA® promotes regenerative healing and prevents haze

Severe Neurotrophic Keratopathy

- May need surgical repair
  - Lamellar keratoplasty
  - Penetrating keratoplasty
  - Sutured multilayer amniotic membrane transplantation
    - Used in defects as deep as 90% of the depth of the stroma
  - Cyanoacrylate glue with a soft bandage contact lens
    - Defects smaller than 2 mm

Ocular Findings Associated with Herpes Family

- Episcleritis
- Scleritis
- SPK
- Pseudodendritic keratitis
- Stromal keratitis
- Uveitis
- Iris atrophy
- Glaucoma
- Vitritis
- Retinitis
- Choroiditis
- Optic neuritis
- CN palsy

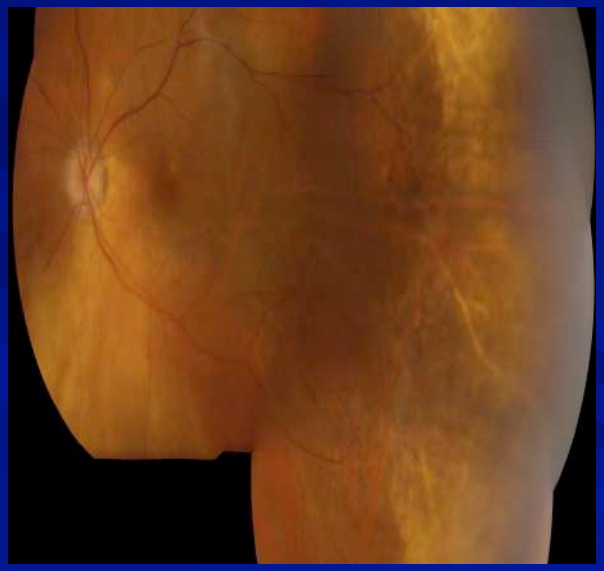


Acute Retinal Necrosis (ARN)

- A rare presentation of herpetic or other viral disease
  - Varicella zoster is most common cause
  - HSV 1-2, CMV, EBV infections
- Characterized by large areas of retinal whitening and necrosis that spreads centripetally with a high rate of accompanying detachment and vascular occlusion
- Historically, ARN was believed to affect healthy adults
  - Increasing evidence suggests that patients who develop ARN have underlying immune dysfunction
- Polymerase chain reaction-based (PCR) analysis of the intraocular fluid is valuable in diagnosis of infectious retinitis
  - Aqueous or vitreal fluid
  - Small sample volume from the anterior chamber is usually sufficient to defect copies of VZV, HSV, CMV, or Toxoplasmosis gondii DNA in patients with infectious retinitis
  - Results within 1 week

Acute Retinal Necrosis (ARN)

- HIV uninfected patients
  - VZV greater than 50%
  - HSV-1 and HSV-2
  - CMV, less common
- Patient with HIV
  - VZV 33%
  - CMV then HSV-1/HSV-2



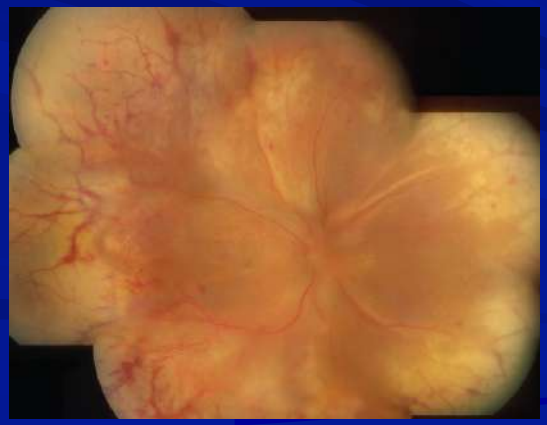
PORN

- Progressive Outer Retina Necrosis (PORN)
  - Starting in posterior pole then outer retina
    - ARN emphasis is peripheral retina
  - Severely immunosuppressed patient
  - HIV positive patient
  - Minimal vitreous involvement despite extensive retina involvement

- It is documented herpetic retinitis

can affect any part of the retina

  - Regardless of immune status



Treatment

- Oral valacyclovir at 2 g TID can achieve systemic levels similar to intravenous acyclovir
- Intravenous acyclovir 10-15mg/kg TID for 5-10 days followed by oral regimen for 6-12 weeks
- Intra-vitreal injection of foscarnet or ganciclovir can be considered
- Laser photocoagulation is controversial
- Management of the retina detachment is both tractional and rhegmatogenous
  - Vitreous condensation and inflammation
  - PVR occurs in up to 75% of patients with ARN

Differential Diagnosis

- Necrotizing retinitis is typically from Herpes Family of viruses but keep in mind:
  - Syphilitic retinitis
  - Toxoplasmic retinochoroiditis
  - Primary vitreo-retinal lymphoma
  - Sarcoidosis
  - Tuberculosis
  - Toxocariasis
  - Fungal or bacterial retinitis/endophthalmitis
  - Behçet's disease

Optometric Education Consultants

Questions and Thank You!

Herpes A to Z
for the Eye Care Provider

Greg Caldwell, OD, FAAO

Primary Eye Care Conference
Pittsburgh

Optometric Education Consultants

Saturday, February 17, 2024