Optometric Education Consultants

Challenges and Controversies in Prescribing Pharmaceuticals

"Discussion Between an Optometrist and Pharmacist"

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Mackinac Island
Optometric Education Consultants
Saturday, August 27, 2022

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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue, RVL, Heru
  - Disclosure: Receive speaker honorariums
- Advisory Board: Allergan, Sun, Alcon, Maculogix, Dompe, Visus, Eyenovia
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- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
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- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes
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Disclosures: Tracy Offerdahl, PharmD

All relevant relationships have been mitigated

- Dr. Offerdahl has the following financial disclosure:
  - Boiron: honorarium, webinar/speaker
- Has not received any assistance from any commercial interest in the development of this course

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Course Design

- To be a discussion between an optometrist and pharmacist
  - As if we were out to dinner having a discussion
- Please use the chat box for your questions

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Branded versus Generic

- FDA definition of a "Generic"
  - Drug product that is comparable to brand/reference/trade drug in dosage form, strength, route of administration, quality, performance characteristics, and indications
- True "Generics": no concerns regarding the safety or efficacy of the formulation compared to the brand
- Generic manufacturers are typically required by the FDA to demonstrate equivalence to GET FDA approval to be listed as a "GENERIC EQUIVALENT"

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Branded versus Generic

- DID YOU KNOW that most ophthalmic solutions are NOT mandated to prove therapeutic equivalence?!?
  - FDA does NOT require pharmacokinetic assays and strict demonstration of human bioequivalence for ophthalmic meds
    - Bioavailability cannot be directly measured in the human eye
- Any product approved prior to 1992 does NOT have to the match the inactive ingredients listed by brand-name manufacturer
  - Generic Drug Enforcement Act (1992): requires generic substitutes to include the same active and inactive ingredients as the brand name drug
  - Excipients that may differ: preservatives, pH adjusters, thickening agents, buffers, etc.

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Branded versus Generic Glaucoma Medications

- Potential problems with generic ocular meds
  - Packaging differences - the strictly regulated packaging and bottle manufacturing for eyedrops in BRAND meds does not exist with generics, resulting it differences in:
    - Bottle material
    - Configuration of dropper
    - Size of eyedrop may be different with generic meds
      - Size variation: 25mcL to 70mcL
        - = potential for differences in efficacy and adverse effects
      - Nano Dropper?

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Nanodropper – microliters?

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It will hopefully get better…

- GDUFA (Generic Drug User Fee Amendment)
  - Established research programs (FDA and outside sources)
  - Hopes to improve methodologies and tools to establishing drug equivalence standards for generics
- Pays PARTICULAR interest to drugs that have:
  - Complex active ingredients, formulations, or dosage forms
  - Complex routes of delivery
  - Complex drug-device combination products
  - Tools and methodologies for bioequivalence and therapeutic equivalence evaluation

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How does the pharmacist decide "Brand" versus "Generic" when they dispense?

- MOST insurance plans mandate or GREATLY encourage patients to use generics
  - Copays are higher for brand/trade names
  - May require prior authorization
- In general, generic drugs are 80-85% less that their Brand name counterparts
- 2011 – Xalatan patent expired
  - Estimated to save patients $1,300+ annually!

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Branded versus Generic

- Branded does drug testing and trials, submitted to FDA
  - Generics do an abbreviated version to FDA
    - Don't have to prove efficacy and safety
- Branded
  - Know the manufacturer
  - Confidence in quality and consistency
- Generics must be in an acceptable range of concentration
- Harder to measure an ophthalmic drug like a systemic medication regarding same concentration, active ingredients, dosage, and route of administration
- Ingredients from other countries with less oversight
- FDA approves the bottle in branded
  - Stability testing, number of drop coming out meet the minimum treatment regimen, how much active ingredient absorbs into the bottle
  - A specific medication is only approved for that one medicine and that one bottle
- Generics
  - Bottles look different
  - Bottle "flexibilities" are different
  - Drop size differ
  - No absorption testing

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Prostaglandin Analogs

- Latanoprost (Xalatan)
  - 8 generic manufacturers
  - ALL of them contain benzalkonium chloride as does the brand
- Bimatoprost (Lumigan) 0.03%
  - 5 generic manufacturers
  - All of them contain benzalkonium chloride as does the brand
- Travoprost (Travatan Z)
  - 4 generic manufacturers

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Beta-Blockers

- Betaxolol (Betoptic S)
  - 2 generic manufacturers – one of two (Akorn) contains benzalkonium chloride and disodium edta
- Carteolol solution (generic only)
  - Preservative free
- Levobunolol (Brand d/c)
  - 2 generic manufacturers – one of two (Bausch Health) contains benzalkonium chloride & edetate disodium & sodium metabisulfite
- Metipranolol (generic only)
  - Preservative free

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Beta-Blockers

- Timolol gel forming solution (Timoptic XE) 0.25 & 0.5%
  - 2 generics (1 of 2 contains benzododecinium bromide)
  - Brand contains tromethamine
- Timolol solution (Timoptic) 0.25 & 0.5%
  - 3 generic manufacturers and brand all contain benzalkonium chloride
- Timolol (Timoptic Ocudose)
  - Preservative free

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Alpha Adrenergic Agonists

- Brimonidine tartrate (Alphagan P)
  - 0.15%
    - 1 generic manufacturer
    - No preservative in brand or generic
  - 0.2%
    - 5 generic manufacturers
    - 2 generics contain benzalkonium chloride (Akorn and Somerset)

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Alpha Adrenergic Agonists

- Apraclonidine (Iopidine)
  - 2 generic manufacturers
  - Both brand and generic contain benzalkonium chloride

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Carbonic Anhydrase Inhibitors

- Brinzolamide (Azopt)
  - 2 generic manufacturers – both brand and generics contain benzalkonium chloride
- Dorzolamide (Trusopt)
  - 5 generic manufacturers – 4 of 5 generic manufacturers contain benzalkonium chloride
  - Brand and Imprimis is preservative free

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Miotics (Direct-Acting)

- Pilocarpine (IsoptoCarpine) 1, 2, & 4%
  - 4 generic manufacturers (3 of 4 contain benzalkonium bromide
  - Brand name and Sandoz generic are free from benzalkonium chloride
- Carbachol and Acetylcholine have no generic equivalents

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Fixed Combinations

- Brimonidine/timolol – Brand only
  - Benzalkonium chloride
- Brinzolamide/Brimonidine – Brand only
  - Benzalkonium chloride
- Dorzolamide/timolol (Cosopt)
  - Brand contains benzalkonium chloride (except Cosopt PF)
  - 5 of 8 generics contain benzalkonium chloride
    - Preservative free generics: Akorn, Aurobindo, Imprimis
- Netarsudil/latanoprost (Rocklatan) – Brand only
  - Benzalkonium chloride

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The Benefits of Generics…

- Research has found a correlation between lower medication cost and improved adherence rates with ocular medications
- Ocular meds are VERY expensive and insurance companies are ALWAYS searching for a cheaper alternative!

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Tips and Pearls to Writing a Glaucoma Prescription

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Tips and Pearls on Prior Authorizations Glaucoma Prescription

- Prior authorizations are inevitable!
- Steps:
  1. Pharmacist processes RX and gets a "reject" that says, "PA required" OR "must try _____1st/must prove medical necessity"
  2. Pharmacist sends electronically to "Cover My Meds" AND prescriber
  3. EVERYONE waits to hear back (1 day to 3 weeks!!)

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Good Rx

GoodRx may be able to find you a lower price than your insurance co-pay. Hundreds of generic medications are available for $4 or even free without insurance.

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ImprimisRx and Others

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Coupon Cards Tips and Pearls

- Manufacturer Discount Cards:
  - These are for BRAND NAME only!
- Good RX: Brand and Generic

- Read the fine print!
  - Expiration dates!
  - Does the patient need to "activate" the card"?
  - How many "fills" will they get?
  - Medicare/Medicaid excluded?

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Glaucoma Medications

- Send to the local pharmacy
- Send to mail in

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Direct Pay Pharmacies Patient and Pharmacy

- We will discuss Xelpros™ latanoprost ophthalmic solution 0.005%
  - It's differences
- Thoughts of being delivered by direct pay between patient and pharmacy
  - Capstan Pharmacy
  - Transition Pharmacy

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Mechanism of Action versus Mechanism of Delivery

Adjuvant

In pharmacology, an **adjuvant** is a drug or other substance, or a combination of substances, that is used to increase the efficacy or potency of certain drugs.

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Inflow versus Outflow

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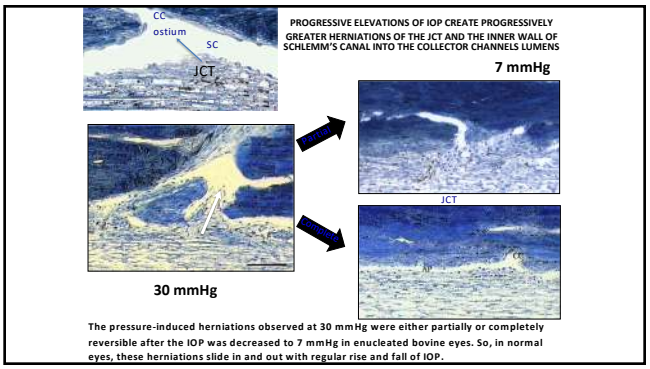

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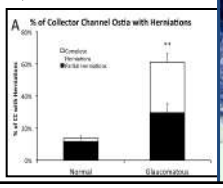
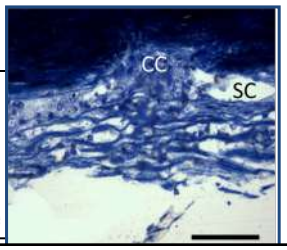
Human eyes with POAG even at 0mmHg, exhibit herniations and many more than in age-matched normal eyes

A: Significantly more herniations of the TM into CC ostia were found in POAG eyes (33 of 54), than in normal eyes (7 of 51) (61% vs. 14%, p<0.0001). In normal eyes, herniations that were present were predominantly partial (86%) rather than complete (14%). In POAG eyes, over half of the larger total number of herniations were complete (52%).

Battista SA, Lu Z, Hofmann S, **Freddo TF**, Overby DR, Gong H: Acute IOP elevation reduces the available area for aqueous humor outflow and induces meshwork herniations into collector channels of bovine eyes. Invest. Ophthalmol. Vis. Sci., 49:5346-52, 2008.





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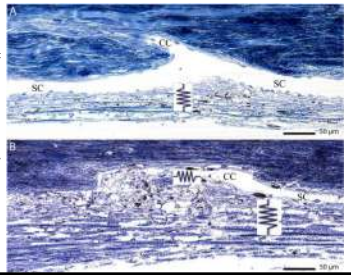
PRINCIPAL NEW FINDING

The presence of herniations, at O mm Hg, suggests they were permanent *in-vivo* obstructions in the ostia of CC, whether partial or complete. These are the only exits from Schlemm's canal. If enough of these 30 channels are fully or even partially blocked, IOP MUST go up.

This study is the first to document the existence of permanent herniations into CC ostia in POAG. Since resistances in series are additive, it could be that these previously unreported permanent herniations, which obstruct CC ostia, represent an additional source of resistance, distal to the trabecular meshwork, in POAG.



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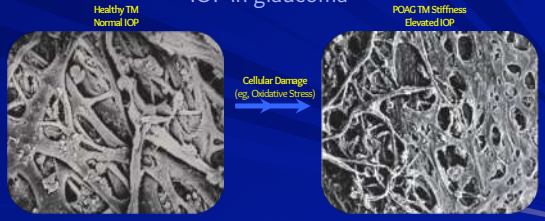
Disease at the TM is responsible for elevated IOP in glaucoma[1,2]



Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.[2]
POAG, primary open-angle glaucoma; TM, trabecular meshwork.
1. He et al. Invest Ophthalmol Vis Sci. 2008;49:1447.
2. Last et al. J Cell Physiol. 2010;224:308.

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The goal is to increase outflow
Glaukos iStent Inject

Aqueous Angiography Before and After Stenting

Alex Huang, MD, PhD

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Blanching Confirms Reliable Access to Multiple Collector Channels – Hydrus Microstent

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Medical Management of Glaucoma...

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...Has Gotten Boring

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Until Recently We Have Some New Pharmaceuticals

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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
- Once daily monotherapy
- Dual mechanism of action
  - Uveoscleral pathway to increase aqueous humor outflow
  - Butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal.
- Ocular adverse events
  - Conjunctival hyperemia, eye irritation, eye pain and instillation site pain
  - Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can occur

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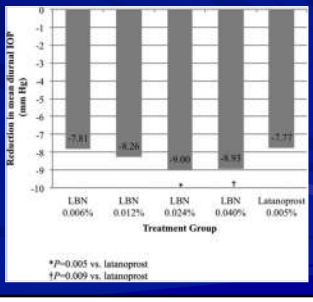
Vyzulta™ (latanoprostene Bunod)



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Xelpros™ (latanoprost ophthalmic solution 0.005%)

- Sun Pharmaceuticals
- Approved September 2018
- Dosage: QD
- Reduce IOP in open-angle glaucoma and ocular hypertension
- Xelpros is the first latanoprost product not formulated with the preservative benzalkonium chloride
  - Potassium sorbate 0.47% - preservative
- Reduces IOP in patients with open-angle glaucoma and ocular hypertension
  - Up to a mean of 6 mm Hg to 8 mm Hg in randomized clinical trials

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Xelpros™ (latanoprost ophthalmic solution 0.005%)

- Not available in pharmacies
- A direct pay between patient and partnering pharmacies
  - Capstan Pharmacy
  - Transition Pharmacy
- Xelpros Xpress offers:
  - No prior authorizations
  - No coupon activation
  - No callbacks
  - Prompt fulfillment and refills
  - $55 for 30 days, $110 for 90 days

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Rhopressa™ 0.02% (netarsudil ophthalmic solution)

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

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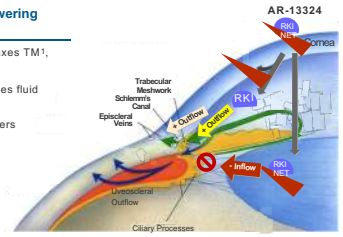
Rhopressa (ROCK-NET Inhibitor) Triple-Action

3 Identified IOP-Lowering Mechanisms

ROCK inhibition relaxes TM[1], increases outflow[1,2]

NET inhibition reduces fluid production[2]

ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]



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

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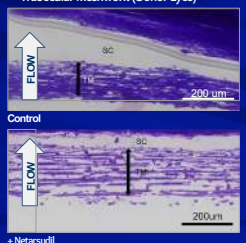
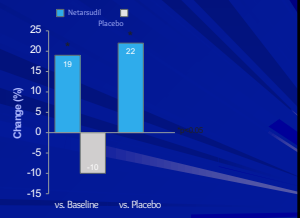
Rhopressa™ 0.02% (netarsudil)

Causes Expansion of TM in Donor Eyes
Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]



TM Outflow Facility (Healthy Volunteers)[2]



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

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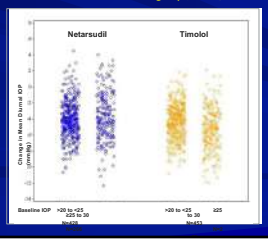
Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

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



Baseline IOP >20 to <25 mmHg

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

Baseline IOP >25 to <30 mmHg

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

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Rhopressa™ 0.02%

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

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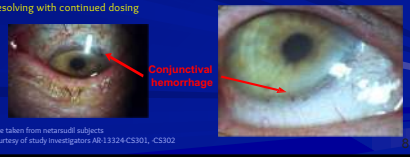
Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

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

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

Self-resolving with continued dosing



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

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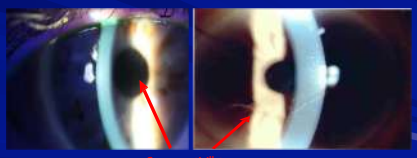
Cornea Verticillata Observed in Phase 3 Studies

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



AR-13324-CS302 netarsudil QD subject

AR-13324-CS302 netarsudil BID subject

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

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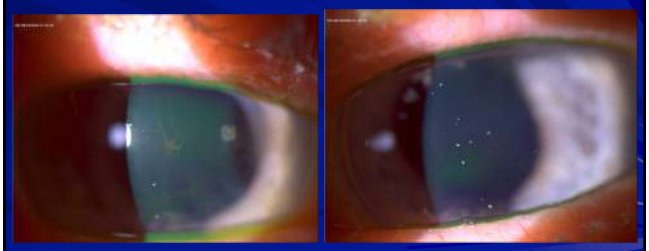
My Experience

OD treated OS gtts



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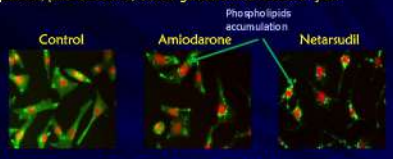
Cornea Verticillata Due to Phospholipidosis

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*

Data on File Based on AR-13324-HP-107
* Rajman R B et al. Surv. Ophthalmol. 2007;52:286-301.

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Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia	Cornea Verticillata	Conjunctival Hemorrhage
• 54.4% TEAE	• 20.9% TEAE	• 17.2% TEAE
• Severity did not increased with continued dosing	• Asymptomatic	• Mild in severity and transient
• Sporadic	• Did not impact visual function	• Self-resolving with continued dosing

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How Will I Use Netarsudil to Treat Glaucoma?

- ** **As a monotherapy in patients who:**
  - * Have concerns about the ocular side effects of PGs
  - * Are intolerant to or have inadequate efficacy with PGs
  - * Need or prefer alternative to beta blockers, alpha agonists, CAIs
- ** **As an adjunct agent:**
  - * Add to a prostaglandin
  - * Add to or alternative to other adjunctive agents
- ** **To improve patient compliance** - fewest number of daily doses is beneficial
- ** **After glaucoma surgery** when desired IOP is not achieved
- ** **As another medical option to help delay or defer glaucoma surgery**

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Glaucoma Drop FDA Approval

- ** Inferiority
- ** Superiority

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Rocklatan™

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

- Approved March 14, 2019
- Aerie pharmaceuticals
- Once-daily eye drop
- One approved PGA combination in USA
  - Inferiority (Timolol) versus Superiority
- Treatment of ocular hypertension and primary open angle glaucoma
  - Board indication

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Bimatoprost SR - Durysta

Sustained Release

- Allergan – Approved March 5, 2020
- Designed to lower IOP for 4 months
  - IOP reduction is approximately 30% from baseline
- Intracameral biodegradable sustained-release implant
  - First in class
- Approved for 1 application
- Indication:
  - Open angle glaucoma
  - Ocular hypertension
- 10 mcg of bimatoprost
- Contraindicated: active or suspected infections, corneal endothelial cell dystrophy, absent or ruptured posterior lens capsule
- Caution in patients with narrow angles

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Bimatoprost SR

Sustained Release

- Contraindications
  - Ocular or periocular infections
  - Corneal endothelial cell dystrophy
  - Prior corneal transplantation
  - Absent or ruptured posterior lens capsule
  - Hypersensitivity
- Warnings and Precautions1
  - Endothelial cell loss: due to possible corneal endothelial cell loss, administration of DURYSTA should be limited to a single implant per eye without retreatment.
  - Corneal adverse reactions: DURYSTA has been associated with corneal adverse reactions and risksare increased with multiple implants. Use caution in patients with limited corneal endothelial cell reserve.
  - Iridocorneal angle: DURYSTA should be used with caution in patients with narrow angles or anatomical angle obstruction.

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Glaucoma Treatment

- Pharmaceuticals
- Laser: SLT/ALT
- MIGS- Minimally Invasive Glaucoma Surgery
  - Avoiding trabs and tubes
- Trabeculectomy
- EX-PRESS glaucoma shunt (Alcon)
- Shunts/valves
- Cyclophotocoagulation

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Optometric Education Consultants

Questions and Thank You!

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