Pharmacology Update

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Disclosure

Has a relevant financial relationship with
Haag Streit, Genzyme, Optovue as a speaker and ZeaVision, Guardion health/VectorVision for research and consultant

The content and format of this course is presented without commercial bias and does not claim superiority and commercial product or service.

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CANT COVER ALL DRUGS FOCUS ON NEW DRUGS AND COMMON

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Acquired Blepharoptosis (Ptosis)

- Abnormal low-lying (drooping) upper eyelid margin with the eye in primary gaze
- Severity depends on degree of eyelid droop[1]
- Can be:
  - Unilateral or bilateral
  - Congenital or acquired

Untreated blepharoptosis can affect:[2-4]

Function
Pupil obstruction, superior visual field deficits

Appearance
Asymmetric or 'sleepy' look

* **References:** 1. Finsterer J. Ptosis: causes, presentation, and management. Aesthetic Plast Surg. 2003;27(3):193–204. 2. Ho SF, Morkevitz A, Sampath R, Burns J. Modified visual field test for ptosis surgery (Leicester Peripheral Field Test). Eye. 2011;25:342–349. 3. Cahill KV, Burns JA, Weber PA. The effect of blepharoptosis on the field of vision. Ophthalmol Plast Reconstr Surg. 1987;3(3):121–125. 4. Richards, HS, Johnson S, Rumsey N, et al. The psychological well-being and appearance concerns of patients presenting with ptosis. Eye. 2014;28(3):296–302.

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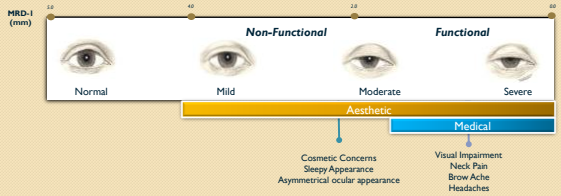
What is Acquired Ptosis ("droopy eyelid")?

Definition: Abnormal low lying upper eyelid that may be non-functional or functional depending on patient symptoms

Causes: Typically slowly progressive and associated with aging, but can also be myogenic, neurogenic, traumatic, or mechanical in nature

Background: Common eyelid disorder affecting adults of all ages especially those over 50



Both non-functional and functional patients may benefit from treatment*

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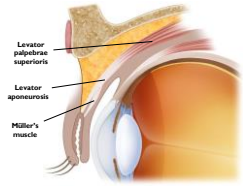
Causes of Blepharoptosis: Congenital vs. Acquired

Congenital blepharoptosis[1,2]

- Typically a result of developmental myopathy of the levator muscle or innervation abnormality

Acquired blepharoptosis[1,3]

- Most often, a result of stretching of the levator muscle or disinsertion of the levator muscle complex (aponeurotic)
- Can also be caused by:
  - Reduced nervous input to the upper eyelid retractor muscles (neurogenic)
  - Injury (traumatic)
  - Excess skin / eyelid heaviness (mechanical)
  - Primary muscle dysfunction, such as myotonic dystrophy (myogenic)



References: 1. Sudhakar P, Yu Q, Kowalak-Lesiak O, Palmer M. Upper eyelid ptosis: revisited. Am J Clin Med. 2009;6(3):9–14. 2. Gunter RL. Blepharoptosis. In: Yanoff M, Duker JS, eds. Ophthalmology. 3rd ed. St Louis, United States Elsevier; 2008. 3. Khoshi M, Vishal JM, Allen RC. A primer on ptosis. Available at: http://webeye.ophth.uiowa.edu/eyeforum/tutorials/Ptosis/Index.htm. Accessed September 27, 2019.

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Acquired Blepharoptosis: Risk Factors

- Acquired blepharoptosis is typically associated with **aging**

An estimated **11.5%** of adults aged 50+ have **blepharoptosis**, and prevalence **increases with age**[1]

In the U.S. population, this corresponds to an estimated **13 million** patients aged 50+ with blepharoptosis in 2020[1,2]*

- Other known risk factors include:
  - **Ocular surgery** (glaucoma, cataract, corneal, strabismus)[3,4]
  - **Contact lens** wear[5-9]
  - **Underlying disease**[10]

* Estimated U.S. population over 50 years of age with ptosis calculated as estimated number of individuals aged 50 and older (U.S. Census) multiplied by 11.5% prevalence observed in study by Sridrahan et al.[1]

References: **1.** Sridharan GV, Tallis RC, Leatherbarrow B, Forman WM. A community survey of ptosis of the eyelid and pupil size of elderly people. *Age Ageing.* 1995;24:21-24. **2.** US Census Bureau, Population Division. Table 9: Projections by sex and age for the United States: 2015 to 2060. NP2014-T9. December 2014. **3.** Wang Y, Lou L, Liu Z, Ye J. Incidence and risk of ptosis following ocular surgery: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol.* 2019;257:397-404. **4.** Godfrey KJ, Korn BS, Kikkawa DO. Blepharoptosis following ocular surgery: identifying risk factors. *Curr Opin Ophthalmol.* 2016;27:31-37. **5.** Hwang K, Kim JH. The risk of blepharoptosis in contact lens wearers. *J Craniofac Surg.* 2015;26:e374-e374. **6.** Kitazawa T. Hard contact lens wear and the risk of acquired blepharoptosis: a case-control study. *Eplasty.* 2013;13:219-224. **7.** Thean JHJ, McNab AA. Blepharoptosis in RGP and PMMA hard contact lens wearers. *Clin Exp Optom.* 2004;87:11-14. **8.** Satariano N , Brown MS, Zwiebel S, Guyuron B. Environmental factors that contribute to upper eyelid ptosis: A study of identical twins. *Aesthet Surg J.* 2015; 35(3):235-41. **9.** Bleyen I, Hiemstra CA, Devogelaere T, van den Bosch WA, Wubbels RJ, Paridaens DA. Not only hard contact lens wear but also soft contact lens wear may be associated with blepharoptosis. *Canad J Ophthalmol.* 2011;46 (4): 333-6. **10.** Finsterer J. Ptosis: causes, presentation, and management. *Aesthetic Plast Surg.* 2003;27(3):193–204.

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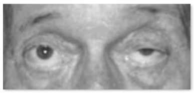
Differential Diagnosis: Neurological Disease

- **Focused neurological examination** should be conducted prior to treating blepharoptosis[1]
- In some cases, blepharoptosis can be a **sign of more serious underlying neurological disease**,[1,2] e.g.:
  - **Horner's syndrome:** mild ptosis associated with ipsilateral pupil constriction, eye redness, and anhidrosis[1,2]
    - Can be secondary to trauma, stroke, or vascular disease
  - **Myasthenia gravis:** unilateral or bilateral ptosis with upper eyelid position variability, often accompanied by diplopia and / or strabismus[1,2]
  - **Chronic progressive external ophthalmoplegia:** symmetric, bilateral ptosis and ophthalmoparesis, with initial presentation typically in a patient's 30s[1,2]
  - **Oculomotor nerve (CN III) palsy:** ptosis associated with ophthalmoplegia, diplopia, and poorly-reactive dilated pupil[1,2]
    - Can be a result of ischemic injury or aneurysm



Ptosis in a patient with myasthenia gravis (Finsterer J. *Aesthetic Plast Surg.* 2003;27(3):193–204).[1]

- CN III, third cranial nerve
- **References:** **1.** Finsterer J. Ptosis: causes, presentation, and management. *Aesthetic Plast Surg.* 2003;27(3):193–204. **2.** Klejch W, Vislisel JM, Allen RC. A primer on ptosis. Available at: http://webeye.ophth.uiowa.edu/eyeforum/tutorials/Ptosis/index.htm. Accessed September 27, 2019.

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Acquired Blepharoptosis

Current Treatment Options and Impact on Patients and Practice

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Treatment Options for Acquired Blepharoptosis

Approach	Key considerations
Rx Eye Drop Oxymetazoline HCl ophthalmic solution, 0.1%	**Pro:** *non-invasive, effective, pharmacologic therapy that can improve visual function and increase upper eyelid elevation*[1] **Con:** *daily use*
Surgery (anterior or posterior approach)	**Pro:** *can improve visual function, QoL*[2] **Con:** *not all patients are good candidates; complication risks (e.g. bleeding, scarring, infection)*[2]
Off-label medication use (e.g. apraclonidine)	**Pro:** *can increase upper eyelid elevation*[4-9] **Con:** *can have unwanted side effects (e.g. pupil dilation, contact dermatitis)*[8]
Non-surgical **mechanical intervention** (e.g. eye crutch, eyelid tape, scleral contact lenses)	**Pro:** *conservative, non-surgical approach to elevating the upper eyelid*[3,10-12] **Con:** *temporary solutions, can cause discomfort*

QoL, quality of life

References: 1. UPNEEQ™ (oxymetazoline hydrochloride ophthalmic solution) 0.1% [Prescribing Information]. RVL Pharmaceuticals, Inc. 2020. 2. Cahill KV, Bradley EA, Meyer DR, et al. Functional indications for upper eyelid ptosis and blepharoplasty surgery: a report by the American Academy of Ophthalmology. Ophthalmology. 2011;118:2510-2517. 3. Finsterer J. Ptosis: causes, presentation, and management. Aesthetic Plast Surg. 2003;27(3):193–204. 4. Kirkpatrick CA, Shriver EM, Clark TE, Kardon RH. Upper Eyelid Response to Topical 0.5% Apraclonidine. Ophthal Plast Reconstr Surg. 2018;34(1):13-19. 5. Lee GN, Lin LW, Mehta S, Freitag SK. Response to phenylephrine testing in upper eyelids with ptosis. Digit J Ophthalmol. 2015;21(3):1-12. 6. Scheinfeld N. The use of apraclonidine eyedrops to treat ptosis after the administration of botulinum toxin to the upper face. Dermatol Online J. 2005;11(1):9. 7. Steinsapir KD, Groth MJ, Boxrud CA. Persistence of Upper Blepharoptosis After Cosmetic Botulinum Toxin Type A. Dermatol Surg. 2015;41(7):833-840. 8. Wijemanne S, Vijayakumar D, Jankovic J. Apraclonidine in the treatment of ptosis. J Neurol Sci. 2017;376:129-132. 9. Garibaldi DC, Hindman HB, Grant MP, et al. Effect of 0.5% apraclonidine on ptosis in Horner syndrome. Ophthal Plast Reconstr Surg. 2006;22(1):53-55. 10. Pullum KW, Whiting MA, Buckley RJ. Scleral contact lenses: the expanding role. Cornea. 2005;24:269-277. 11. Shah-Desai SD, Aslam SA, Pullum K, et al. Scleral contact lens usage in patients with complex blepharoptosis. Ophthalmic Plast Reconstr Surg. 2011;27:95-98. 12. Katsoulos K, Rallatos GL, Mavrikakis I. Scleral contact lenses for the management of complicated ptosis. Orbit. 2018;37:201-207.

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Introduction to:
Oxymetazoline HCl ophthalmic solution, 0.1%

Formulation, Mechanism of Action and Clinical Data

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ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation and headache.

DRUG INTERACTIONS

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.

Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

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Oxymetazoline HCl ophthalmic solution, 0.1%

Formulation

- Study Name: RVL-1201
  Brand Name: Upneeq™
  Contains the active ingredient **oxymetazoline HCl**
- Preservative-free balanced salt solution containing hypromellose

Dosing

- One drop administered topically **to ptotic eye(s), once per day**

Formulation	
Oxymetazoline HCl 0.1% (0.035 mg / drop)	Active ingredient
Hypromellose	Hydrophilic polymer
Water Calcium chloride Magnesium chloride Potassium chloride Sodium acetate Sodium chloride Sodium citrate	Balanced salt solution components

Upneeq (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

- Oxymetazoline is a **well-established pharmacologic agent**, with a history of use as an OTC nasal spray (0.05% solution), OTC eye drops (0.025% solution), and RX topical cream (1% cream)

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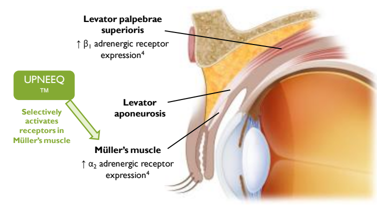
Mechanism of Action

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



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

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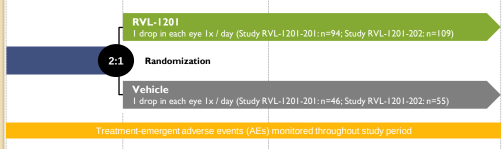
Phase 3 Efficacy Study Design

Day -7 to -3
- Screening
- LPFT, MRD-1
- Vital signs, ophthalmic exam*
- IOP, ophthalmoscopy

Treatment day 1
- Baseline and randomization
- LPFT (pre-dose and 6 hours)
- MRD-1 (pre-dose, 5 min & 15 min [Study RVL-1201-202 only], 2 hours, 6 hours)
- Vital signs, ophthalmic exam*

Treatment day 14 (± 3 days)
- LPFT (2 hours)
- MRD-1 (pre-dose, 5 min & 15 min [Study RVL-1201-202 only], 2 hours, 6 hours)
- Vital signs, ophthalmic exam*

Treatment day 42 (± 3 days)
- MRD-1 (incl. 5 & 15 min in Study RVL-1201-202 only)
- Vital signs, ophthalmic exam*
- Tolerability assessment
- IOP, ophthalmoscopy



*Includes Snellen visual acuity, pupil diameter, corneal fluorescein staining, slit lamp exam

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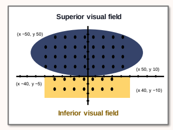
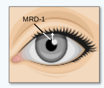
Phase 3 Efficacy Endpoints

Study RVL-1201-201 and Study RVL-1201-202

Primary efficacy endpoint
- Change from baseline in the number of points seen in the top 4 rows on the **Leicester Peripheral Field Test (LPFT)**
- Assessed at screening, treatment day 1 (baseline and 6 hours post-drug instillation), and treatment day 14 (2 hours post-drug instillation)



Secondary efficacy endpoint
- Change from baseline in **Marginal Reflex Distance (MRD-1)**
- Assessed at screening, treatment day 1, treatment day 14, and treatment day 42 (end of study)



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Efficacy Population

Combined Efficacy Studies (RVL-1201-201, RVL-1201-202)

Subject demographics and baseline characteristics, combined efficacy studies (RVL-1201-201 and RVL-1201-202)

	RVL-1201 (n=203)	Vehicle (n=101)
Age, years		
Mean (SD)	64.1 (13.4)	63.3 (14.7)
Min, max	20, 92	14, 85
Sex, n (%)		
Female	151 (74.4%)	71 (70.3%)
Male	52 (25.6%)	30 (29.7%)
Race, n (%)		
White	177 (87.2%)	92 (91.1%)
Black	18 (8.9%)	6 (5.9%)
Asian	6 (3.0%)	3 (3.0%)
American Indian	2 (1.0%)	0
Ethnicity, n (%)		
Not Hispanic / Latino	170 (83.7%)	84 (83.2%)
Hispanic / Latino	33 (16.3%)	17 (16.8%)

- 97.4% of subjects **completed** all visits
  - RVL-1201 group: 97.5%
  - Vehicle group: 97.0%
- Overall **compliance with treatment** was 97.8%
  - RVL-1201 group: 98.1%
  - Vehicle group: 97.2%

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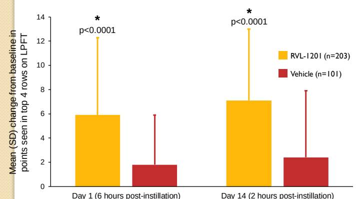
Primary Efficacy Endpoint: Improvement on the LPFT

Combined Efficacy Studies (RVL-1201-201, RVL-1201-202)



- Increase in points seen on LPFT = **improvement in superior visual field**

* vs. vehicle, from an ANCOVA model with study and treatment as fixed factors and baseline score as a covariate
- LPFT, Leicester Peripheral Field Test.

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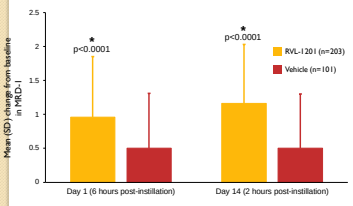
Secondary Efficacy Endpoint: Improvement in MRD-1

Combined Efficacy Studies (RVL-1201-201, RVL-1201-202)



- Significantly greater elevation of the upper eyelid was seen with RVL-1201 than with vehicle

* vs. vehicle, from an ANCOVA model with study and treatment as fixed factors and baseline score as a covariate
• MRD-1, Marginal Reflex Distance

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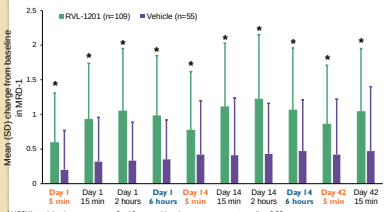
Secondary Efficacy Endpoint: Improvement in MRD-1

Efficacy Study RVL-1201-202



Significant effect vs. vehicle at all time points, including **5 minutes** (rapid onset) and **6 hours** (sustained effect) after drop application

*Please note: The 5 minute time point was only measured in efficacy study RVL-1201-202 and not in study RVL-1201-201

* vs. vehicle, from an ANCOVA model with treatment as a fixed factor and baseline score as a covariate; all p<0.05
• MRD-1, Marginal Reflex Distance

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RVL-1201 Safety: Most Common Adverse Events

Combined Safety Population

TEAEs reported for ≥ 2% of subjects in any treatment group (RVL-1201-001, RVL-1201-201, RVL-1201-202, and RVL-203)

	RVL-1201 (n=375)*	Vehicle (n=193)
Eye disorders		
Punctate keratitis	13 (3.5%)	4 (2.1%)
Conjunctival hyperemia	11 (2.9%)	1 (0.5%)
Dry eye	9 (2.4%)	1 (0.5%)
Vision blurred	8 (2.1%)	0
General disorders and administration site conditions		
Instillation site pain	8 (2.1%)	0
Investigations		
Vital dye staining cornea present	8 (2.1%)	4 (2.1%)
Nervous system disorders		
Headache	8 (2.1%)	2 (1.0%)

* Includes n=360 subjects who received RVL-1201 once daily for at least 6 weeks and n=15 subjects who received RVL-1201 once daily for 2 weeks

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Summary: Efficacy and Safety

- Met both primary and secondary efficacy endpoints in phase 3 studies
  - Once-daily RVL-1201 resulted in significant improvement of the upper visual field (LPFT) and upper eyelid elevation (MRD-1) vs. vehicle
  - Upper eyelid elevation was rapid and sustained, with significant improvement evident within 5 minutes of instillation in one study

    *Please note: The 5 minute time point was only measured in efficacy study RVL-1201-202 and not in study RVL-1201-201
- Clinical studies also demonstrated RVL-1201's favorable safety and tolerability profile

• LPFT, Leicester Peripheral Field Test; MRD-1, Marginal Reflex Distance

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PRESBYOPIA DRUGS EMERGING DRUGS

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CURRENT HYPOTHESIS OF PRESBYOPIA
1 BILLION PEOPLE AFFECTED

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Aging in the Ciliary Muscle

- *Loss* of muscle fibers and *increase* in connective tissue
- The contractile force does NOT decrease; it increases and is at a maximum at the age presbyopia is manifest

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Aging in the Lens Capsule- Fisher theory

- Thickness of the lens capsule increases from 11µm at birth to 20 µm at 60 years then decreases slightly thereafter
- Force transmitted per unit thickness decreases by half at age 60
- Increased thickness compensates for the loss of elasticity
- The capsule also gets more brittle

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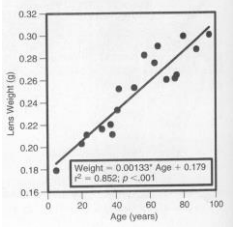
Growth of the Lens

- Continues throughout life
- Linear mass increase of more than 1.5x over the human life span
- Even the equatorial diameter increases



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Growth of the Lens (cont 2)

- When removed from the eye (no zonular forces):
  - Young lenses become accommodated
  - Older lenses don't change shape

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Hardness of the Lens

- A more than four-fold, exponential increase over the life span
  - Doesn't stop at age 50
- The lens substance must remain sufficiently pliable so capsular forces can act on it to flatten it (unaccommodated) and curve it (accommodated)
- **This in itself can account for loss of accommodation with increasing age**

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Lenticular Sclerosis

- The crystalline lens gets harder with increasing age
- Most commonly articulated explanation

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Emerging therapies for presbyopia

- Pinhole effect / Depth of focus effect
- Changing the lens rigidity

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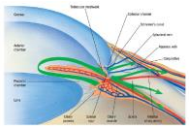
Pilocarpine: Mechanism of action



- Cholinergic muscarinic receptor agonist
- Strong pupillary miosis
- Anatomic relationship between anterior tendons of ciliary muscle and
  - Scleral spur
  - Peripheral cornea
  - Trabecular meshwork
  - Inner wall of schlems canal

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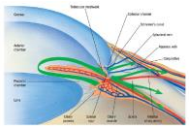
Mechanism of action



- Contraction of ciliary muscle causes
  - Unfolding of meshwork
  - Widening of Schlemm's canal

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Pilocarpine

- Main difference low dose is utilized compared to glaucoma therapy <1%
- Side effects
  - Stinging
  - Burning
  - Ciliary spasm, temporal or supraorbital headache and induced myopia, possibly lower in this case as low dose pilocarpine

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Various pilocarpine therapies

- Abbvie/ Allergan Gemini I and II 750 participants
  - 3 or more lines mesopic high contrast distance corrected near visual acuity (DCNVA)
  - Side effects in less than 3% cases
- Orasis Phase II- 166 participants Phase II 300 participants
  - 3 or more lines improved in DCNVA phase II
- Eyenovia
  - Novel microdose –dispenser
  - Studies underway will check 1% and 2% pilocarpine

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Pilocarpine+ Phentolamine

Testing long lasting combination therapy

- Phentolamine is non-selective Alpha-1 and Alpha-2 adrenergic antagonist 0.75% (evening dose)
- Pilocarpine 0.4% morning dose

- This should synergistically inhibit iris dilator muscle
- Along with activation of Iris sphincter

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Presbyopia therapies-LiquidVision

- Aceclidine is a parasympthomimetic cholinergic muscarinic receptor agonist.
- 47% gained 3 or more line DCNVA
- 92% gained two or more lines in 1 hour
- Lasts 7 hours

- A combination with tropicamide is also investigated to relax accommodation so younger people can use it and provides more "depth of vision"

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Fixed combination Carbachol/Brimonidine

- Brimochol
- Carbachol very potent miotic much more than pilocarpine, longer lasting
- Brimonidine
  - prevents pupil dilation
  - May inhibit muscle contraction
  - also decreases redness "eye whitening"

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Lipoic acid choline ester chloride

- Novartis
- Acts on the disulfide bonds between lens protein
- Hydrolyzing the bonds would soften the lens
- Restore accommodation
- Early studies –DCNVA phase 1/2
  - 8.1 letter improvement drug
  - 4.3 letter improvement placebo

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- Phase 2
- Early presbyopes used it
- Three month BID dose
- 6.1 letter improvement active
- 4.5 letter improvement placebo

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Vuity FDA approved
Pharmacology and Mechanism of Action

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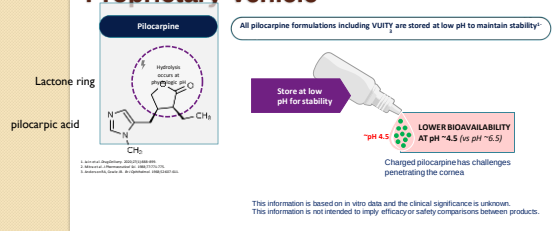
VUITY is a Formulation of Pilocarpine HCl (1.25%) Ophthalmic Solution Delivered With pHast™ Technology – a Proprietary Vehicle



This information is based on in vitro data and the clinical significance is unknown.
This information is not intended to imply efficacy or safety comparisons between products.

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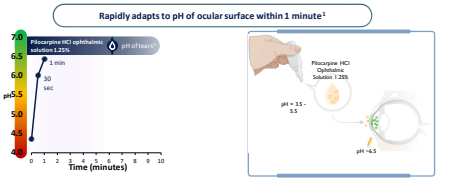
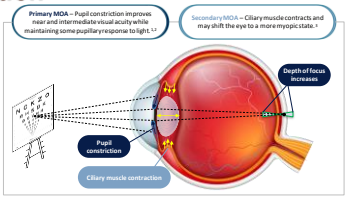
pHast™ Technology – Time to Adapt the pH of the Drop to Match the Physiologic pH of the Tear Film



This information is based on in vitro data and the clinical significance is unknown.
This information is not intended to imply efficacy or safety comparisons between products.

45

Mechanism of Action of Pilocarpine HCl Ophthalmic Solution



46

BRIMONIDINE TARTRATE 0.025%

47

Brimonidine Tartrate 0.025%

- Decreases redness
- Up to 8 hours
- Does it work… sure it does we all have tried it…
- Do you feel itching…after use… allergic reaction?
- Brimonidine 0.1% glaucoma therapy
- Higher doses generic 0.15% or 0.2%

48

Brimonidine 0.15% or 2%

- Induces significant miosis
- Can help post op decrease of glare aberrations etc…
- Pupillary miosis

49

Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-021-05297-8

CATARACT

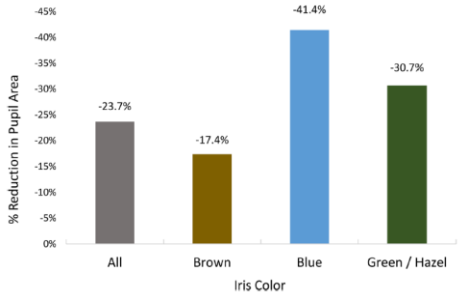
Effect of over-the-counter brimonidine tartrate 0.025% ophthalmic solution on pupil size in healthy adults

Mitra Nejad[1] · Shawn R. Lin[1] · Linda H. Hwang[1] · Mark Landig[1] · Saba Al-Hashimi[1] · John D. Bartlett[1]

Table 2 Pupillary miosis with brimonidine 0.025% instillation

	Total	Pre-instillation (mm)	Post-instillation (mm)	Difference (mm)	Reduction in pupil area (%)	*P* value
Iris color (eyes)						
All	56	7.28	6.36	−0.91	−23.7%	p < 0.0001
Brown	40	7.24	6.58	−0.67	−17.4%	p = 0.005
Blue	10	7.46	5.71	−1.75	−41.4%	p = 0.001
Green/hazel	6	7.23	6.02	−1.22	−30.7%	p = 0.08
Iris color groups						
Dark (brown)	40	7.24	6.58	−0.67	−17.4%	Dark vs. light p < 0.0001
Light (blue, green, hazel)	16	7.38	5.83	−1.55	−37.6%	

50



51

Anti-VEGF and IOP

- Anti-vascular endothelial growth factor (VEGF) agents has dramatically changed the management of ocular diseases
- associated with macular edema, providing improved visual outcomes and a favorable safety profile
- ranibizumab, bevacizumab, pegaptanib and aflibercept and are commonly used in the treatment of diabetic macular edema, neovascular age-related macular degeneration and other pathologies characterized by retinal or choroidal neovascularization
- Less known fact there is a spike in IOP post injection typically returning to baseline in 1 hour
- Very rarely long-term spike in pressure 6-14.8%

52

Why is there an IOP spike with anti-VEGF?

- Volume of drug injected
- Associated factors repeated injections
- Prolonged treatments
- Mechanisms
  - Direct toxic effect of anti-VEGF on TM
  - Injury of TM from large volume
  - Inflammation secondary to anti-VEGF
  - Mechanical blockage of TM

53

DO WE PRETREAT PATIENT?

54

Why should we?

- RNFL defects after long term treatment and no glaucoma have been reported
- IOP does increase significantly after an injection

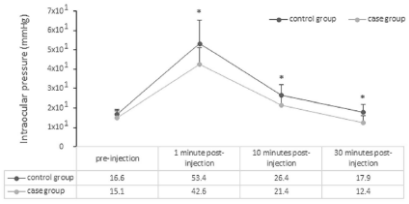
55

ORIGINAL PAPER

Prophylactic effect of brinzolamide–brimonidine fixed combination on intraocular pressure spikes after intravitreal anti-VEGF injections

Maria Dettoraki · Eleni Rapti · Dimitrios Fragkos · Ioannis Theiopoulos · Anthi Legaki · Alexandra Gkounta · Despina Anyfantaki · Frini Riga

2 hour before injection



56

Can other medications be utilized?

- Apraclonidine 1%
- Brimonidine timolol fixed combination
- Dorzoalamide tomolol fixed combination

57

Current consensus

- None
- prophylactic use of hypotensive medications only in patients with glaucoma
- Some recommended their routine use in both glaucomatous and non-glaucomatous eyes
- Whereas others have proposed IOP checking in all patients and treating accordingly.
- Topical prophylactic treatment cannot prevent the immediate IOP rise

58

ANGLE CLOSURE

59

Medical treatment- Goals

- Lower intraocular pressure
- Alleviate pain
- Clear cornea
- Prevent synechiae

60

Intravenous medications

- Acetazolamide 500mg intravenous
- Intravenous Mannitol

- Best therapy however is not always available in clinics

61

Treatment protocol-Acute angle closure- ABC procedure

- Alpha -2 agonist- Brimonidine
- Beta blocker- Timolol (caution in asthmatics) or Betaxolol
- Carbonic anhydrase inhibitor – Dorzolamide (Caution sulpha allergy contraindication)

- Each medication given every 15 minutes

62

Oral medications

- Oral Carbonic anhydrase inhibitor
- Two tablets of 250 mg acetozolamide (Caution sulpha allergies contraindication)
- Works good when patient can retain medication - Vomiting common with angle closure glaucoma

63

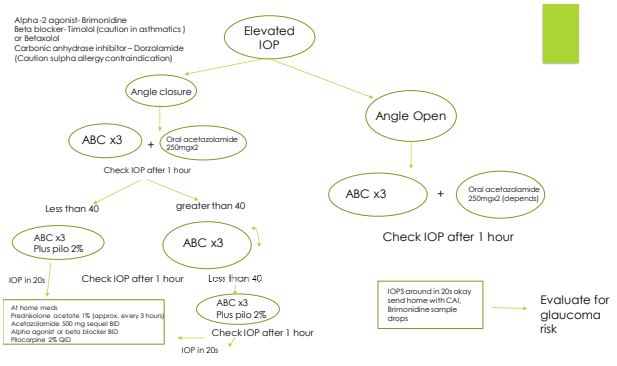
- Check intraocular pressure after 1 hour if lower
- Add Pilocarpine every 15 minutes for 45 minutes and repeat the procedure
- Seek ophthalmologist opinion-refer patient

64

Take home medication

- Prednisolone acetate 1% q1-6 hours (approx every 3 hours)
- Acetazolamide 500 mg sequel BID
- Alpha agonist or beta blocker BID
- Pilocarpine 2% QID

65



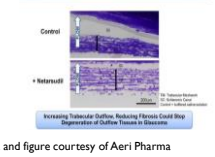
66

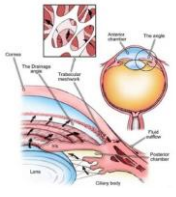
RHOKINASE INHIBITORS

67

Mechanism of action

- Changes to trabecular meshwork-cytoskeletal modulating drugs



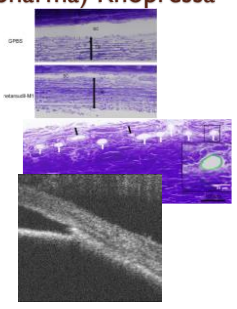


Data and figure courtesy of Aeri Pharma

68

Netarsudil (AERI pharma) Rhopressa™

- Another class of ROCK-inhibitor Small-molecule
- Alter TM cells
- Alters norepinephrine transporter (NET)-
  - NET inhibitor to lower aqueous production ???
- Changes episcleral venous pressure



69

Elevated Rho-kinase activity in TM cells increase cell contraction and stiffness[1,2]

1. Rao et al. Exp Eye Res. 2017;158:23. 2. Lin et al. J Ocul Pharmacol Ther. 2018;34:40.

9

70

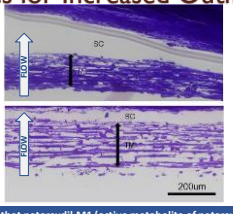
Rho-kinase inhibitors relax TM cells and reduce fibrosis[1,2]

1. Rao et al. Exp Eye Res. 2017;158:23. 2. Lin et al. J Ocul Pharmacol Ther. 2018;34:40.

9

71

Netarsudil Causes Expansion of TM in Donor Eyes, Opening Spaces for Increased Outflow

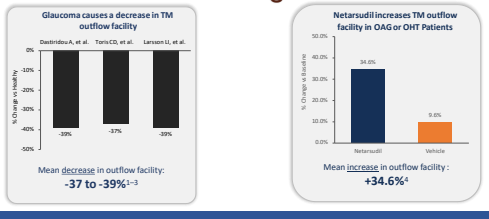


Light microscopy showed that netarsudil-M1 (active metabolite of netarsudil) caused expansion of the trabecular meshwork tissue

Morphology of the TM in perfused human donor eyes was examined using light microscopy. Images were taken using a 20× objective along the inner wall of the SC. TM, trabecular meshwork; SC, Schlemm's canal.
Ren R, et al. *Invest Ophthalmol Vis Sci.* 2016;57(14):6197–6209.

72

Netarsudil Has a Targeted IOP-Lowering Effect on Trabecular Outflow in the glaucomatous TM



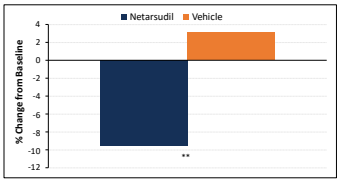
Netarsudil demonstrated a ~35% increase in TM outflow facility

IOP, intraocular pressure; TM, trabecular meshwork.; OAG, open angle glaucoma; OHT, ocular hypertension
1. Dastiridou A, et al. *Invest Ophthalmol Vis Sci.* 2013;54:4571–4577. 2. Toris CB, et al. *J Glaucoma.* 2002;11:253–258. 3. Larsson LI, et al. *Arch Ophthalmol.* 1995;113:283–286. 4. St A, et al. Presented at The Association for Research in Vision and Ophthalmology 2019 Annual Meeting (ARVO 2019); April 28–May 2, 2019; Vancouver, BC, Canada.

73

Netarsudil significantly decreased EVP in patients with POAG or OHT

- In an aqueous humor dynamics study, 20 subjects with POAG or OHT were randomized to netarsudil ophthalmic solution 0.02% administered to one eye and vehicle (placebo), administered to contralateral eye for 7 days
- EVP was measured using a custom-designed slit-lamp mounted computerized venomanometer
  - An inflatable bulb was placed over an episcleral vein and pressure automatically increased
  - Vessel collapse was recorded and synchronized with pressure transducer measurements
  - Venous pressure was assumed to be the applied pressure that initiated venous collapse

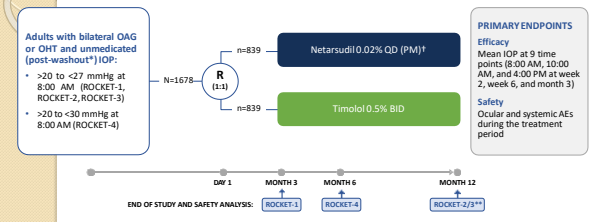


Netarsudil demonstrated ~10% change from baseline in mean diurnal EVP

**P<0.01
EVP, episcleral venous pressure; IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma;
St A, et al. Presented at The Association for Research in Vision and Ophthalmology 2019 Annual Meeting (ARVO 2019); April 28–May 2, 2019; Vancouver, BC, Canada.

74

ROCKET Studies: Design[1,2]



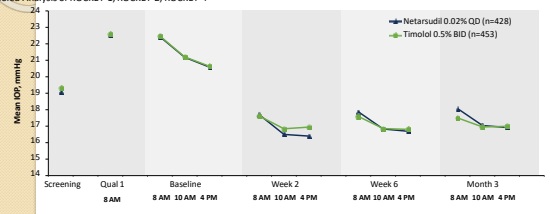
*The minimum washout period was 4 weeks for patients using prostaglandin analogs or beta-adrenoceptor antagonists prior to study entry, 2 weeks for those using adrenergic agonists, and 5 days for those using muscarinic agonists or carbonic anhydrase inhibitors. †To maintain masking, patients randomized to once-daily netarsudil received placebo in the morning and active drug in the evening. **ROCKET-2 and -3 included a netarsudil BID arm.
AE, adverse event; BID, twice daily; IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension; QD, once daily; R, randomization.
1. Singh AJ, et al. Presented at the American Society of Cataract and Refractive Surgery Annual Meeting (ASCRS 2018); May 15–19, 2018; Boston, MA. 2. Fechtner RD, et al. Presented at the American Society of Cataract and Refractive Surgery Annual Meeting (ASCRS 2018); May 15–19, 2018; Boston, MA.

75

Once-Daily Netarsudil Was Non-Inferior to Twice-Daily Timolol at All Nine Time Points Through Month 3

Baseline IOP <25 mmHg, Pooled Per-Protocol Population

Pooled Analysis of ROCKET-1, ROCKET-2, ROCKET-4 [1,2]



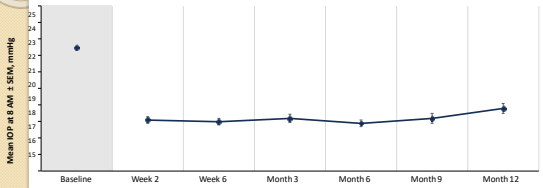
BID, twice daily; IOP, intraocular pressure; NS, not significant; QD, once daily; Qual, qualification.
1. Fechtner RD, et al. Presented at the American Society of Cataract and Refractive Surgery Annual Meeting (ASCRS 2018); May 15–19, 2018; Boston, MA.
2. Data on file, Aerie Pharmaceuticals, Inc.

76

Netarsudil Maintained Efficacy Through 12 Months

Analysis of ROCKET-2

Patients With Baseline IOP <25 mmHg Treated With Netarsudil 0.02% QD (n=129)[1]



IOP was only collected at 8 AM at months 6, 9, and 12 months as a safety measure.
IOP, intraocular pressure; QD, once daily; SEM, standard error of the mean.
1. Serle J, et al. Presented at The Association for Research in Vision and Ophthalmology 2018 Annual Meeting (ARVO 2018); April 29–May 3, 2018; Honolulu, HI.

77

Ocular Adverse Events Reported in ≥5% of Patients

Preferred Term Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (n=839) n (%)	Timolol 0.5% BID (n=839) n (%)
Eye disorders		
Conjunctival hyperemia	456 (54.4)	87 (10.4)
Cornea verticillata (corneal deposits/corneal opacity)	175 (20.9)	2 (0.2)
Conjunctival hemorrhage	144 (17.2)	15 (1.8)
Vision blurred	62 (7.4)	12 (1.4)
Lacrimation increased	60 (7.2)	5 (0.6)
Erythema of eyelid	57 (6.8)	6 (0.7)
Visual Acuity reduced	44 (5.2)	13 (1.5)
General disorders and administration site conditions		
Instillation site pain	167 (19.9)	181 (21.6)
Instillation site erythema	76 (9.1)	13 (1.5)
Investigations		
Vital dye staining cornea present	79 (9.4)	64 (7.6)

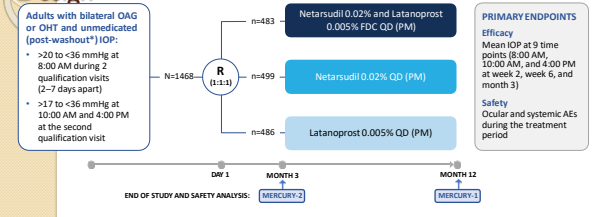
BID, twice daily; QD, once daily.
Singh AJ, et al. Presented at the American Society of Cataract and Refractive Surgery Annual Meeting (ASCRS 2018); May 15–19, 2018; Boston, MA.

78

Netarsudil 0.02% and Latanoprost 0.005% FDC QD Overview

79

MERCURY Studies: Design



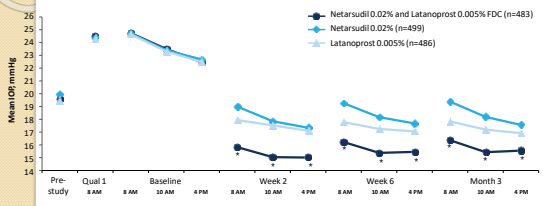
*The minimum washout period was 4 weeks for patients using prostaglandin analogs or beta-adrenoceptor antagonists prior to study entry, 2 weeks for those using adrenergic agonists, and 5 days for those using muscarinic agonists or carbonic anhydrase inhibitors.
FDC, fixed-dose combination; IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension; QD, once daily; R, randomization.
Asrani S, et al. Adv Ther 2020; 37:1620–1631.

80

Netarsudil and Latanoprost FDC Achieved Statistical Superiority Over Individual Components at All Time Points Over 3 Months

Pooled Analysis of MERCURY-1 and MERCURY-2

- Efficacy in this pooled analysis (ITT population) was consistent with the individual studies

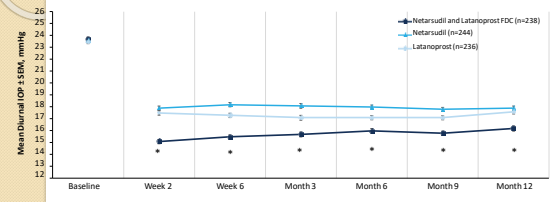


*P<0.0001 vs netarsudil and latanoprost.
P-values derived from analyses of covariance (ANCOVA, least-squares mean).
FDC, fixed-dose combination; IOP, intraocular pressure; ITT, intent-to-treat; Qual, qualification.
Asrani S, et al. Adv Ther 2020; 37:1620–1631

81

Netarsudil and Latanoprost FDC Maintained Superior Efficacy Through 12 Months

Analysis of MERCURY-1 (ITT Population, n=238)

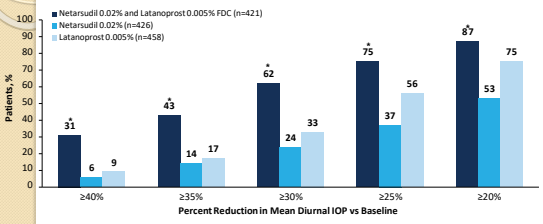


*P<0.001 vs latanoprost and netarsudil.
FDC, fixed-dose combination; IOP, intraocular pressure; ITT, intent-to-treat; SEM, standard error of the mean.
Data on file, Aerie Pharmaceuticals, Inc.

82

Significantly Greater Proportion of Patients Achieved Target Percent IOP Reduction with Netarsudil and Latanoprost FDC vs. Monotherapy

Analysis of MERCURY-1 and MERCURY-2 ITT Pooled Efficacy Population Who Completed 3 Months

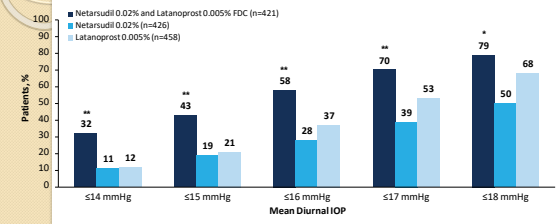


*P<0.0001 vs netarsudil and latanoprost.
FDC, fixed-dose combination; IOP, intraocular pressure.
Asrani S, et al. Adv Ther 2020; 37:1620–1631

83

Significantly Greater Proportion of Patients Achieved Absolute IOP Targets with Netarsudil and Latanoprost FDC vs. Monotherapy

Analysis of MERCURY-1 and MERCURY-2 ITT Pooled Efficacy Population Who Completed 3 Months



*P<0.0001 vs netarsudil and P<0.05 vs latanoprost; **P<0.0001 vs netarsudil and latanoprost.
FDC, fixed-dose combination; IOP, intraocular pressure.
Asrani S, et al. Adv Ther 2020; 37:1620–1631

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Ocular Adverse Events Reported in ≥5% of Patients

Pooled Analysis of MERCURY-1 and MERCURY-2

- The majority of ocular AEs were mild and similar to the individual components

Patients, n (%)	Netarsudil 0.02%/ and Latanoprost 0.005% FDC (n=482)	Netarsudil 0.02% (n=498)	Latanoprost 0.005% (n=488)
Eye disorders			
Conjunctival hyperemia	283 (58.7)	234 (47.0)	108 (22.1)
Cornea verticillata	74 (15.4)	58 (11.6)	0
Conjunctival hemorrhage	52 (10.8)	72 (14.5)	5 (1.0)
Eye pruritus	37 (7.7)	23 (4.6)	5 (1.0)
Visual acuity reduced	25 (5.2)	21 (4.2)	9 (1.8)
Lacrimation increased	25 (5.2)	28 (5.6)	1 (0.2)
Punctate keratitis	17 (3.5)	27 (5.4)	14 (2.9)
General disorders and administration site conditions			
Instillation site pain	97 (20.1)	83 (16.7)	33 (6.8)
Instillation site discomfort	25 (5.2)	23 (4.6)	5 (1.0)

AE, adverse event; FDC, fixed-dose combination. Four patients received a treatment different from their randomized treatment resulting in 1 fewer patient in each of the netarsudil/latanoprost and netarsudil groups, and 2 additional patients in the latanoprost group.
Asrani S, et al. Adv Ther 2020; 37:1620–1631

85

Once-Daily Netarsudil 0.02% and Latanoprost 0.005% FDC - Summary

- Only FDC with a PGA in the US
  - Complimentary MOAs: ROCK inhibitor (TM outflow) + PGA (Uveoscleral outflow)
- Superiority over individual components:
  - Lowered IOP by up to 2.5 mmHg more than latanoprost
  - Stable efficacy through 12 months
- Significantly greater proportion of patients achieving both target percent IOP reductions and absolute IOP targets in all pre-specified categories
  - 62% achieved a ≥30% reduction from baseline (≈2x more than latanoprost alone)
  - Approximately a third achieved IOPs of ≤14 mmHg (≈3x more than latanoprost alone)
- Associated ocular AEs were mild and tolerable, similar to its individual components
  - Conjunctival hyperemia was the most common ocular AE

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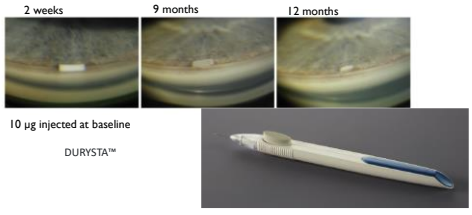
SUSTAINED RELEASE

87

Bimatoprost Sustained-Release Implants for Glaucoma Therapy: 6-Month Results From a Phase I/II Clinical Trial

RICHARD A. LEWIS, WILLIAM C. CHRISTIE, DOUGLAS G. DAY, E. RANDY CRAVEN, THOMAS WALTERS, MARINA BEJANIAN, SUSAN S. LEE, MARGOT L. GOODKIN, JANE ZHANG, SCOTT M. WHITCUP, AND MICHAEL R. ROBINSON, FOR THE BIMATOPROST SR STUDY GROUP



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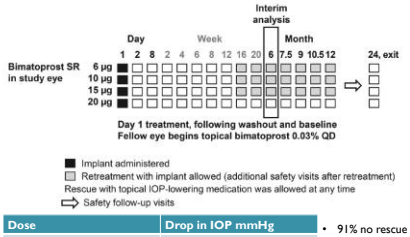

Dose	Drop in IOP mmHg
6 µg	7.2
10µg	7.4
15 µg	8.1
20 µg	9.5
Fellow eye topical bimatoprost 0.3%	8.4

- 91% no rescue tx needed-16 weeks
- 71% no rescue tx needed-6 months
- All doses comparable to bimatoprost 0.03% at 16 weeks

89

Omidenepag Isopropyl 0.002%

New drug

90

Pharmacologic Characterization Omidenepag Isopropyl 0.002%

- Pro drug hydrolyzed in eye during corneal penetration to Omidenepag (Active form)
- Omidenepag hydrolyzed form of Omidenepag Isopropyl 0.002% lowers IOP
- Highly selective prostanoid EP2 receptor agonist

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Pharmacologic Characterization Omidenepag Isopropyl 0.002% cont..

- EP2 receptors found in various parts of brain (cerebral cortex, thalamus, hypothalamus), spinal cord and eye
- EP2 which is a G-protein coupled receptor is expressed in cornea, conjunctiva, sclera, trabecular meshwork, lens , iris, ciliary body, choroid and retina
- Decreases IOP via both conventional and unconventional pathways
- Phase III AYAME Study- Non inferior to Latanoprost
- Does not change Iris color*
- Does not change orbital fat*

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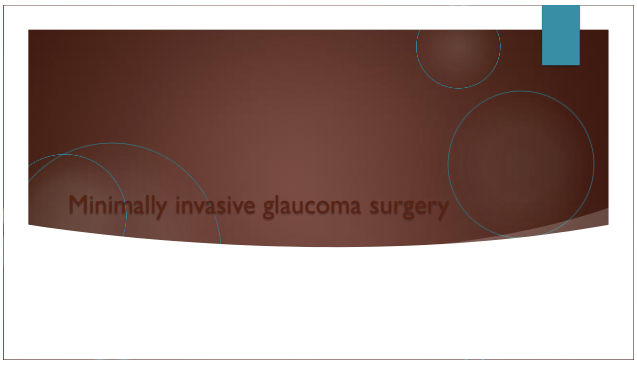
Omidenepag Isopropyl 0.002%

- Approved once daily for glaucoma and OHT Japan 2018
- Approved once daily for OAG and OHT Korea 2019, Taiwan 2020
- November 2021 (Delayed)

93



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Sustained-Release Pharmaceutical: **iDose TR**

- Alternative to topical medications to address non-adherence & other medication drawbacks
- Titanium implant (1.8 mm x 0.5 mm) designed for continuous drug delivery directly into anterior chamber, membrane designed to elute specially formulated travoprost
- Designed to provide long duration intracameral pharmaceutical; secure, anchored design; facile implantation and exchange upon drug depletion
- AMA approved Cat III codes for implantation, removal and re-implantation of drug delivery system into anterior chamber, effective 7/21

iDose TR is not approved by the FDA and limited by US law to investigational use

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iDose TR US Multicenter Phase II Trial: Study Design

Key Aspects of Study Design
154-patient, multi-center, randomized, double-blind trial
Evaluated 2 iDose models with two different travoprost elution rates, compared to topical timolol ophthalmic solution, 0.5%
Primary efficacy endpoint of non-inferiority to topical timolol
Subjects diagnosed with mild to moderate OAG or ocular hypertension, on 0 to 3 meds with baseline IOP between 21 mmHg and 36 mmHg
Additional medications were added if IOP was above 18 mmHg

iDose TR is not approved by the FDA and limited by US law to investigational use

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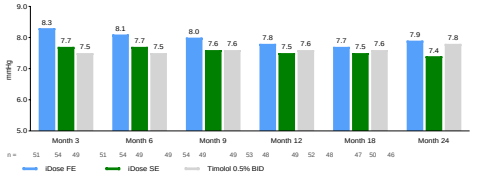
iDose US Multicenter Phase II Trial: **24 Month Outcomes**

PHASE 2 CLINICAL DATA AT 24 MONTHS*

Average Reduction in IOP



*Calculated using all IOP observations through each data point weighted equally, no imputations for mandated medications

iDose TR is not approved by the FDA and limited by US law to investigational use

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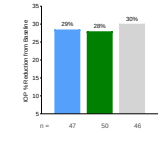
iDose US Multicenter Phase II Trial: **24 Month Outcomes**

Average IOP % Reduction from Baseline

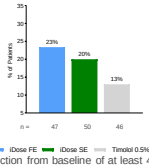
PHASE 2 CLINICAL DATA AT 24 MONTHS*



Average IOP reduction from baseline was 29% and 28% for the fast- and slow-release *iDose TR* arms, respectively, versus 30% for the timolol control arm at 24 months

PHASE 2 CLINICAL DATA AT 24 MONTHS*

Proportion of Subjects with ≥ 40% IOP Reduction from Baseline



IOP reduction from baseline of at least 40% was shown in 23% and 20% of patients for the fast- and slow-release iDose TR arms, respectively, versus 13% of patients for the timolol control arm at 24 months

*Calculated using all IOP observations through each data point weighted equally, no imputations for mandated medications

iDose TR is not approved by the FDA and limited by US law to investigational use

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Prostaglandin Analogs-FP Agonists

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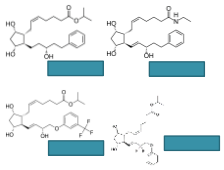
Various prostaglandin analogs

- Latanoprost (formerly XALATAN 0.005%, Pfizer, New York, NY)
- Travoprost (TRAVATAN Z 0.004%, Alcon, Fort Worth, Tex.)
- Bimatoprost (LUMIGAN 0.03%, Allergan, Irvine, Calif.)
- Tafluprost (ZIOPTAN, Akorn Illinois)



100

Prostaglandin analogs (PGs)

- All PGs have similar structure
- They are prodrugs of Prostaglandin $F_{2\alpha}$
- Converted by corneal enzymes into its active form
- Activates the $F_{2\alpha}$ prostaglandin receptors on ciliary body

101

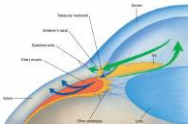
Pro drugs

- Inactive outside activates to a different structure by biological tissue
- PGA oil soluble outside. Easily absorbed by epithelium
- Enzymes changes it to acidic form –soluble by water can pass through stroma and enters anterior chamber

102

Mechanism of action

- Increases outflow through uveoscleral pathway.
- Small percentage increase in conventional outflow.
- Does not reduce aqueous production
- Mechanism not fully understood



103

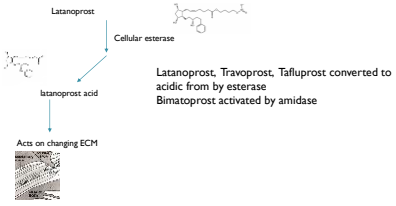
Mechanism of action cont…

- Two theories

1. Relaxation of ciliary muscle
2. Dilated spaces between cliliary muscle bundles

104

Mechanism of action



105

Contraindications

- Allergic to this drug
- Pregnant or nursing caution
- Pediatric – less effective
- Unclear PGs and ocular inflammation

106

PGs and inflammation

- Not first choice
- Some reports : association of PGs (latanoprost) and cystoid macular edema
- Caution: PGs CME, iritis or hepes simplex keratitis, or immediate post-op
- Don't use- cases with complicated surgery, CME or risk of CME, torn posterior capsules.

107

Treatment

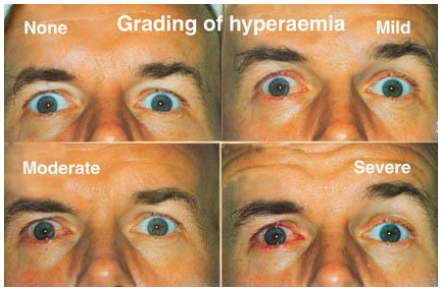
- Once daily evening
- Helps prevent morning spike in pressure
- Should not be utilized more than once daily
  - Twice daily less effective than once daily

108

Side effects

- Conjunctival hyperemia
- Iris color change
- Eyelash changes
- Skin pigmentation
- Deepening of upper eye lid sulcus (DUES)

109



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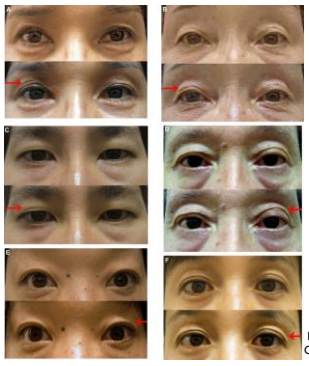


Maruyama et al., Clinical Ophthalmology 2013:7 1441–1446

111

What protocol to follow if glaucoma patient needs cataract surgery?

- Stop prostaglandin analog one (1) month prior to surgery
- Put patient on other IOP lowering medications
- Have surgery
- 1 month after surgery when out come successful restart prostaglandin analog

112

PGs and systemic side effects

- None
- Prostaglandin analog reaches systemic circulation
- Metabolized by liver
- Elimination by kidneys
- Half life 17 minutes in human plasma
- In contrast to timolol no effect on blood pressure

113

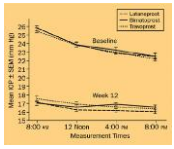
PGs IOP reduction

- Pooled data (n=1389)
- Latanoprost reduces mean diurnal IOP 7.9 mmHg (about 32 %)
- Timolol 1. 6 mmHg less than latanoprost

114

Comparison of PGs

- All are similar
- Effective in all ethnic groups
- PGs better than timilol in African Americans
- No loss of effect over time.



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Additivity

- PGs increase outflow
- So adding it with drugs that decrease production of aqueous makes sense
- Adding a drug that increases conventional outflow makes sense

116

PROSTAGLANDIN NON-RESPONDERS

- IOP ≤ 10% reduction rate

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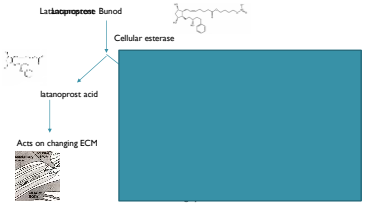
Latanoprostene Bunod- Bausch and Lomb

- Latanoprostene bunod (LBN, BOL-303259-X) is a nitric oxide (NO)-donating prostanoid FP receptor agonist

118

Mechanism of action



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LATANOPROSTENE BUNOD FDA AND INTERNATIONAL TRIALS

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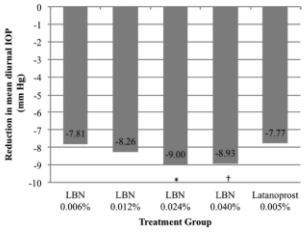
A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study

Robert N Weinreb,[1] Tuyen Ong,[2] Baldo Scassellati Sforzolini,[2] Jason L Vittitow,[2] Kuldev Singh,[3] Paul L Kaufman,[4] for the VOYAGER study group



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Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

The APOLLO Study

Robert N. Weinreb, MD,[1] Baldo Scassellati Sforzolini, PhD,[2] Jason Vittitow, PhD,[2] Jeffrey Liebmann, MD[3]

Sample size 420 (387 completed)
Timolol Maleate 0.5% or Latanoprostene Bunod 0.024%
IOP measured at 8 AM , 12 noon and 4 PM at week 2, 6, and 3 months

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Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

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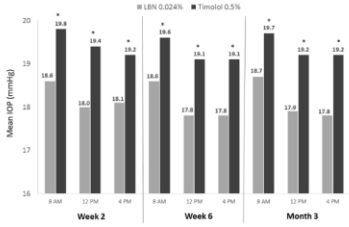

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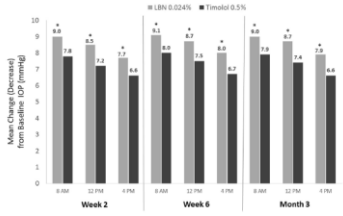

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Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension

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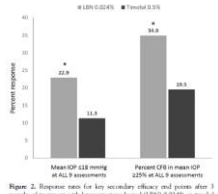

Figure 2. Response rates for key secondary efficacy end points after 3 months of treatment with latanoprostene bunod (LBN) 0.024% or timolol 0.5% (intent-to-treat [ITT] population with last observation carried forward [LOCF]). CFB = change from baseline; IOP = intraocular pressure. *P ≤ 0.005 versus timolol.

125

Efficacy of Latanoprostene Bunod 0.024% Compared With Timolol 0.5% in Lowering Intraocular Pressure Over 24 Hours

JOHN H.K. LIU, JOHN R. SLIGHT, JASON L. VITTITOW, BALDO SCASSELLATI SFORZOLINI, AND ROBERT N. WEINREB

- Twenty five patients
- 43-82 years
- Ocular hypertensive or early glaucoma

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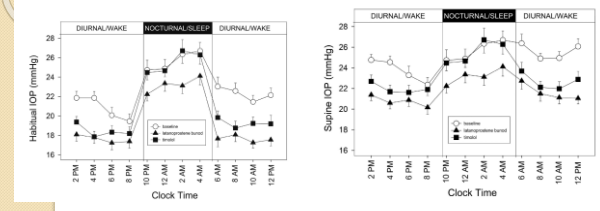
Sitting and supine IOP



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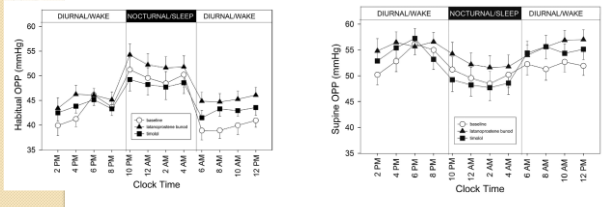
Sitting and supine Ocular Perfusion Pressure



128

Adv Ther (2014) 31:1612–1627
DOI 10.1007/s12325-014-0185-7

ORIGINAL RESEARCH

Long-term Safety and Efficacy of Latanoprostene Bunod 0.024% in Japanese Subjects with Open-Angle Glaucoma or Ocular Hypertension: The JUPITER Study

Kazuhide Kawase · Jason L. Vittitow · Robert N. Weinreb · Makoto Araie · For the JUPITER Study Group

Adverse events	LBN 0.024%	
	Study eye ($N = 130$) *n* (%)	Treated fellow eye ($N = 126$) *n* (%)
≥1 ocular AE	76 (58.5)	78 (61.9)
≥1 treatment-related ocular AE	62 (47.7)	61 (48.4)
Eye disorders		
Conjunctival hyperemia[a]	23 (17.7)	21 (16.7)
Growth of eyelashes	21 (16.2)	21 (16.7)
Eye irritation	15 (11.5)	15 (11.9)
Eye pain	13 (10.0)	13 (10.3)
Iris hyperpigmentation	5 (3.8)	5 (4.0)

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Adverse events	LBN 0.024%	
	Study eye ($N = 130$) *n* (%)	Treated fellow eye ($N = 126$) *n* (%)
Blepharal pigmentation	4 (3.1)	4 (3.2)
Blepharitis	3 (2.3)	3 (2.4)
Eye pruritus	3 (2.3)	3 (2.4)
Asthenopia	3 (2.3)	2 (1.6)
Conjunctival hemorrhage	2 (1.5)	3 (2.4)
Punctate keratitis	3 (2.3)	2 (1.6)
Trichiasis	3 (2.3)	2 (1.6)
Cataract	1 (0.8)	3 (2.4)
Hordeolum	1 (0.8)	3 (2.4)
Foreign body sensation in eyes	2 (1.5)	1 (0.8)
Visual impairment	1 (0.8)	2 (1.6)
Vitreous floaters	1 (0.8)	2 (1.6)
Chalazion	0 (0.0)	2 (1.6)

130

Summary findings of Latanoprostene Bunod (LBN)

- LBN Statistically superior IOP lowering vs. Latanoprost (> 1 mmHg) in a Phase II study
- LBN Statistically superior IOP lowering vs. Timolol in 17/18 time points in two Phase III studies
- LBN marked and sustained (24h) IOP lowering in healthy normotensive subjects
- LBN No significant AEs (average 5-7% hyperemia rates across all studies)
- LBN Nocturnal IOP significantly lower than baseline and significantly lower than timolol maleate

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BASICS OF ANTIBIOTICS

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Antibiotics

- Most prescribed empirically
  - Broad spectrum vs. tailored therapy (cultures)
- Considerations
  - Safety (eg. drug-drug interactions)
  - Individual patient factors
  - Cost
  - Site of infection
  - Organism (or likely organism) causing infection

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Antibiotics

- Begin with the correct diagnosis
- Treat with minimal adverse effects
- Avoid tapering oral antibiotics (don't sub-optimal dose drug leads to drug resistance)
- Try to avoid using same oral agent twice in a short period
  - Not so much a concern with topicals

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Antibiotics

- Prophylaxis
  - Topicals used prophylactically all the time
    - Eg. Corneal injuries
  - Only a few cases in which orals are prescribed prophylactically
    - Eg. True orbital blowout fracture

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Penicillins

- Inhibit cell wall synthesis
- Most effective on actively replicating bacteria
- Bactericidal
- More G(-) and less G(+) in later generations
- Should be penicillinase resistant (second generations, resists hydrolysis of beta-lactam ring in penicillin by bacterial enzyme)
- Contraindications (penicillin allergy, cephalosporin crossover sensitivity)

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Penicillins usual dosage

- Dicloxacillin
  - 250mg q.i.d. x 1 week
  - 500mg b.i.d. Pregnancy category B
- Augmentin
  - Amoxicillin/clavulanate
  - 500/875/1000mg b.i.d. x 1 week
  - Pregnancy category B

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Cephalosporins

- Very similar mechanism to penicillins (inhibition of cell wall synthesis)
- Crossover hypersensitivity with penicillins common
- More G(-) and less G(+) in later generations
- Bactericidal
- Like penicillins, may alter normal flora (b-complex or active probiotic additionally good idea)

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Cephalosporins

- Keflex (cephalexin)
  - 500mg b.i.d.
  - 1st generation (more G(+) coverage)
  - Pregnancy category B

Can get nephrotoxicity from concomitant use of cephalosporin and aminoglycoside (gentamicin, tobramycin, etc.)

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Macrolides

- Inhibit protein synthesis in bacterial ribosomes
- Do not bind to mammalian ribosomes (generally safe)
- Contraindications
  - Hypersensitivity
  - Drug interactions (quite a few with Erythromycin)
  - Clarithromycin should be avoided in pregnancy

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Macrolides

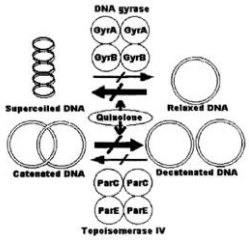
- Erythromycin
  - Typically 500mg q.i.d. x 1 week
  - Many drug interactions (check PDR, etc.)
  - Pregnancy category B
    - Probably the biggest reason macrolides have a place in eye care

141

Fluoroquinolones

- Fluoroquinolones act by **inhibiting enzymes involved in bacterial DNA synthesis**
- Specifically, fluoroquinolones inhibit DNA gyrase and topoisomerase IV
- DNA gyrase tends -primary target for -Gram- negative organisms topoisomerase IV -primary target -Gram-positive bacteria.
- These enzymes are essential for bacterial DNA replication, thereby enabling these agents to be both specific and bactericidal.

142



143

- First generation quinolone- nalidixic acid limited Gram negative
- Second generation quinolone- pipemidic acid better gram negative
- Third generation- fluorination at R6 hence term fluoroquinolones- Norfloxacin Gram negative and limited gram positive
- Further structural changes Cyclopropyl ring at R1 position- Ciprofloxacin

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- Addition of Six-member pyridobenzoxazine between R1 and R8 led to development of ofloxacin
- Both ciprofloxacin and ofloxacin expanded activity against gram –positive
- levofloxacin (active enantiomer of ofloxacin)- better gram positive effect

145

- Fourth generation- addition of methoxy side chain at R8 position- Gatifloxacin (methyl group of piperazinyl ring), Moxifloxacin (bulky bicycle ring R7 position)
  - Improved activity in streptococcus and staphylococcus species
  - Added anerobic activity

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Fluoroquinolones oral common dose

- Levofloxacin (Levoquin)
  - Typically 500mg or 750mg q.d. x 1 week
  - By far most common oral
- Ciprofloxacin (Cipro)
  - Typically 250mg or 500mg b.i.d. x 1 week

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- Broad spectrum (though resistance exists)
- Good for true penicillin allergies
- Not recommended for children / pregnant
  - bone issues, risk of Achilles tendon rupture

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Mechanisms of resistance

- Alterations in drug target enzymes
  - Mutations in DNA gyrase or topoisomerase IV
  - DNA gyrase most commonly mutation is fluoroquinolone-resistant gram-negative bacteria
  - Drug affinity decreased to gyrase-DNA complex
- Alterations in access to enzymes
  - Drug must cross cell wall or cytoplasmic membrane
  - Membrane associated efflux pumps- pump drug out faster- low level resistance
  - Gram-negative- decreased outer membrane proteins-thus decreased drug diffusion

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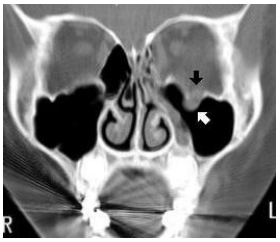
22yoM

- Injury OS 4 days ago
- Pain, diplopia
- 20/30 OD 20/25 OS
- PERRL(-)APD
- Dilated retinal exam normal
- EOM's – vertical diplopia / OS constriction

Case courtesy Ben Casella OD

150

22yoM



http://www.e-radiography.net/radpath/f/blowout_fracture/blowout_fracture.htm

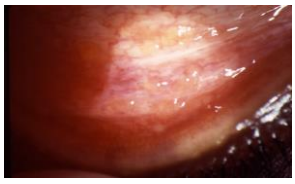
151

22yoM

- Keflex 500mg b.i.d.
- Orbital blowout fracture is one of the few instances when an ORAL antibiotic is prescribed prophylactically

152

(Hint: topicals are not very useful in this case)

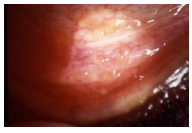


Courtesy: Brian Hall, OD, FAAO and Gary Oliver, OD, FAAO

153

Macrolides

- Azithromycin
  - Zithromax or "Z pak" (500mg q.d. on day one, then 250mg q.d. on days 2-5)
  - 1g single dose for *Chlamydia trachomatis* (repeat regular dose if needed)



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Ophthalmic use of antibiotics

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Disease diagnosed by patients

- External hordeolum "Stye" –most common
- Treated or not it will disappear eventually
- Patients have tried various things
- Usually painful or ugly and hence to office visit
- Acute Staphylococcal infection of glands of Zeis or Moll
- Maybe associated with blepharitis

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Management

- Epilation of a couple of involved lashes
- Hot compress indeed helps
- Antibiotic like Erythromycin q.i.d. acute phase prevents spread
- Can continue for a week after that b.i.d.
- Recurrent cases look for causes and cultures if necessary.
- Check for diabetes if recurrent
- Awkward conversation about improving hygiene

157

Internal Hordeolum

- Staphylococcal infection of meibomian glands.
- Mild cases hot compress sufficient
- Moderate cases- Oral antibiotics
  - Cephalexin 500 mg b.i.d. x 7-14 days (caution penicillin allergy) text book
  - Augmentin 500 mg b.i.d 5-7 days (caution penicillin allergy)
  - Azithromycin 500mg day 1 and 250 mg for next 4 days…far more practical (caution macrolide allergy)
  - Oral fluoroquinolone levofloxacin 500mg once daily x 7 -10 days
  - Surgical removal is an option

158

Chalazion

- Spontaneous or follow episode of internal hordeolum
- Sterile lipogranulomatous inflammation of meibomian gland
- Often associated with saborrhea or seborrheic blepharitis
- Oral or topical antibiotics wont work
- Hot compress and lid massage q.i.d 2-4 weeks if small
- Injection of Kenalog-10, 0.1ml –through skin if pointing outward, through conj in pointing inward
- May have to repeat 1 more time (caution skin depigmentation)
- Persistent surgical excision

159

BLEPHARITIS

160

Blepharitis

- The term *blepharitis* encompasses a variety of ocular manifestations dealing with redness and inflammation surrounding the lid margin and eyelashes.
- chronic blepharitis is associated with poor hygiene or with conditions and occupations leading to dirty hands.
- Bilateral condition: symptoms are itching, burning, scratchiness, foreign-body sensation, excessive tearing, and crusty debris around the eyelashes that is worse in the morning.
- Anterior - seborrheic
- Posterior - MGD

161

- Slit lamp examination may

1. reveal lid erythema, collarettes, trichiasis,
2. plugged meibomian glands, conjunctival injection, and,
3. occasionally, superficial punctate keratitis on the lower third of the cornea.
4. Some patients may also demonstrate an associated conjunctivitis with papillary hypertrophy of the palpebral conjunctiva.

162

Treatment

- Mild cases Lid hygiene scrubbing with baby shampoo
- Moderate cases –Pharmacological treatments
  - Gentamycin Tobramycin
  - Erythromycin
  - Polymyxin B
  - Bacitracin
  - Bid-qid drops or ointment
- Severe cases oral treatment

163

Doxycycline

- Widely used for MGD
- Typically 50mg to 100mg q.d. for a few months and implement omega 3 FA supplementation concurrently
- 20mg available
- It is a tetracycline
  - Not for kids, pregnant, nursing, pt's on blood thinners, risk of breast cancer???????
  - Increased sensitivity to sunlight –skin rash, itching, discoloration, severe burn- resolve 10-14 days after discontinuing

164

Flare-up

- Red inflamed eyelids
- Steroid antibiotic combination
  - Tobradex (Tobramycin + dexamethasone)
  - Zylet (tobramycin + loteprednol)
  - q.i.d 1-2 weeks then just antibiotic

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TOPICAL ANTIBIOTICS

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Acute bacterial conjunctivitis

- S. aureus most common
- Culture… almost never unless history unclear or severe to very severe (possibly gram negative)
- Broad spectrum antibiotics
- Polytrim (trimethoprim –polymyxin B)
- Gentamycin
- Tobramycin (q.i.d x 7 days)
- Fluroquinolones (ciprofloxacin, moxifloxacin (q.i.d. x7days besifloxacin t.i.d. x 7 days)

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Severe with risk of preseptal cellulitis or otitis media

- Oral antibiotic amoxicillin or fluoroquinolone
- Steroid antibiotic combination if pseudo membrane or true membranes

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Allergic conjunctivitis

- Seasonal allergic conjunctivitis
  - Spring and early fall
  - Pollen, grass pollen, ragweed
  - Type I IgE-mediated reaction
- Perennial allergic conjunctivitis
  - Indoors all year long

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OTC meds- patient has already tried

- Opcon-A, Visine-A and Naphcon-A contain an H1- receptor antihistamine (either antazoline or pheniramine) and a vasoconstrictor (either naphazoline or tetrahydrozaline).
- The antihistamine component competitively blocks the H1 receptors on the nocioceptive type-C nerves of the mucosal membranes.
- The result is a significant decrease in ocular itching but little effect on ocular redness or swelling. The vasoconstrictor component works on the conjunctival blood vessels to decrease redness.

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Issues with OTC

- Duration of action is low so multiple dosing needed
- If a patient came to you and you gave OTC chances are they have tried it…
- Rebound conjunctivitis

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Medications

1. Topical antihistamines- competitive inhibition- second line. Does not stabilize mast cells.
   1. **emedastine difumarate (Emadine)**
   2. **levocabastine HCl (Livostin)**

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Mast cell stabilizers

Mast cell stabilizers- reduce degranulation and thus histamine that mast cells release.

Prevention-in those you can predict occurrence like seasonal allergies- Example

- Mast cell stabilizers
  - pemirolast potassium (Alamast)
  - cromolyn sodium (Crolom)
  - lodoxamide tromethamine (Alomide)
  - nedocromil sodium (Alocril)

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Antihistamine/Mast cell stabilizers

- 1st line therapy
- Dual acting
- olopatadine HCl (Patanol/Pataday/Pazeo)
- azelastine HCl (Optivar)
- Epinastine (Elestat)
- Ketotifen (Zaditor)
- Alcaftadine (Lastacaft)

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Steroids and ocular allergies

- Once more common for stubborn severe allergic conjunctivitis
- Loteprednol etabonate (alrex)
- Safe
- IOP spikes extremely rare
- If used use 7-10 days when symptoms or signs are severe along with Anti/histamine mast cell stabilizer.

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Oral medications for allergies

- Not as effective
- Common misconception among patients and some doctors…
- Needed when systemic symptoms are too much
- Mucosal dryness – secondary to inhibition of muscarinic receptors

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ANTERIOR UVEITIS

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Anterior non granulomatous uveitis

- Acute, unilateral, usually idiopathic
- Small keratic precipitates, no iris nodules
- Responds great to corticosteroids
- First time healthy patient, no major investigations needed. Even if done you will not find a cause- idiopathic
- Slit lamp evaluation, dark adapt make sure its not posterior or intermediate uveitis or intermediate with spill over anterior- good BIO views with scleral depression or contact lens fundus examination

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Treatment

- Mild (1+ cell and flare) 1% prednisolone acetate 3-4 times a day, cycloplegic for pain and prevents synechia – cyclopentolate 1-2% 3-4 times or 1% homatropine
- Moderate 1% prednisolone acetate every 2-3 hours with 5% homatropine q.i.d
- Severe 1% prednisolone acetate every 1-2 hours, 1% atropine b.i.d.
- Follow-up 1-7 days based on severity
- Steroids used greater than 2 weeks must measure IOP
- Taper steroids to once resolved or minimal cells

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Anterior uveitis- investigate if

- Bilateral
- Granulomatous
- Recurrent
- No indications of systemic disease

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Suggested work-up anterior uveitis

- Complete blood cell count (CBC)
- Erythrocyte sedimentation rate (ESR)
- Antinuclear antibody test (ANA)
- Rapid plasma regain (VDRL)
- Fluorescent treponemal antibody
- Chest X-ray
- Lyme titer
- HLA-B27 test

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