ADVANCES IN THERAPEUTICS FOR OCULAR DISEASE

JESSICA STEEN OD, FAAO, DIPL ABO

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FINANCIAL DISCLOSURES

- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point
- Advisory Board-Bausch and Lomb, Santen, Peripherex, Ocuphire, Ocuterra
- Shareholder-Clearside Biomedical (<0.01% ownership)

- *All relevant relationships have been mitigated*

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Making an Impact

Filling an unmet need

Common conditions

Rare disease

Providing additional options

Novel products

Repurposed molecules

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Framework for Development

Orphan drug designation (1983)

<200,000/year
Federal grants and contracts to support clinical trials
Tax credits-25% of clinical testing costs (reduced from 50% in 2018)
Exclusive right to market the drug for 7 years from date of marketing approval
Maximum flexibility to the design of pivotal trials
More likely to be single arm trials, un-blinded and use surrogate endpoints

Fast Track Designation (1988)

Drugs which fill an unmet clinical need
More frequent communication with FDA
Rolling review
Eligible for accelerated approval and priority review
Surrogate measures
2 tiered system-standard (10 months) vs. priority (6 months)

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Framework for Development

PDUFA (1992)

Authorized the FDA to collect fees from drug companies-important role in expediting drug approval process
Is there industry influence when 45% of the FDA's budget is funded through user fees?

Application fee: $3,117,218 (2022) + program fee ($369,413)
Either 10 months; or 6 months if granted priority review

When the FDA takes too long or too little time to review a drug→criticism
Balance between regulation and efficiency

Remember, the FDA doesn't guarantee safety of a product
It ensures that the data presented is credible and ensures benefit with acceptable risks

Balance of safety and efficacy

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How do you stay up to date?

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HOW DO YOU STAY UP TO DATE?

Medscape OPHTHALMOLOGY | MedPulse

AMD and Retinal Disease

Gene Therapy Shows Potential for RPE65-Related Retinal Dystrophy
Medscape Medical News

With Approval Pending, Pegcetacoplan Phase 3 Results Mixed
Medscape Medical News

Glaucoma

Normal-Tension Glaucoma Linked to Alzheimer's Risk
Medscape Medical News

Pediatric Ophthalmology

Pediatricians Urged to Check for Vision Problems After Concussion
Medscape Medical News

Drops Help Pink Eye in Kids, No Antibiotic Necessary?
Medscape Medical News

Eyewire News

06.09.2023
FDA Approves Novaliq's Cyclosporine Eye Drop Vevye for Treatment of Dry Eye Disease

06.08.2023
Reduction of Eyedrop Volume for Topical Ophthalmic Medications with the Nanodropper Bottle Adaptor

06.08.2023
Bausch + Lomb Announces New Scientific Data and Analyses Featuring Consumer, Vision Care and Pharmaceuticals Will Be Presented During Optometry's Meeting

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BREAK DOWN

- IOP raising agents
- IOP lowering agents
- Anterior segment
- Posterior segment

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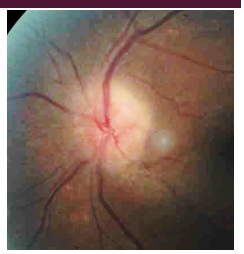
CASE

- 72 year old female
- Woke up with vision loss in the left eye yesterday morning
  - No ocular medications, no systemic medications
  - No headache, scalp tenderness, nausea, malaise, change to appetite
- BCVA: 20/25 OD; CF @ 2 ft OS
  - 3+ APD OS
- PCIOL OU, IOP 12mmHg OD and OS



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NOW WHAT?

- Unilateral disc edema
  - DDx? ***First, think "where?"…then "what?"***
    - Optic neuritis
    - GCA
    - Medications (i.e. sildenafil, amiodarone)
    - Compressive, infiltrative optic neuropathy
    - Neuroretinitis
    - Impending CRVO
    - NAION

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NOW WHAT?

- Does this patient need:
  - 1) Emergent laboratory evaluation
    - *Tests?*
      - *CBC with differential, and platelets CRP, Sed Rate (ESR)*
  - 2) Emergent neuroimaging

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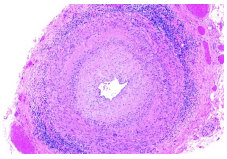
GIANT CELL ARTERITIS

- Idiopathic, **multisystem** inflammation
  - Affects medium and large vessels (internal elastic lamina)
- Upregulation of **IL-6** pathway
  - Infiltration by T cells, macrophages, histiocytes, plasma cells, multinucleate giant cells
  - Leads to occlusion and collapse of the vessel lumen = **ischemia**



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GCA TREATMENT

- **Steroids**
  - Typical initial pulse (methylprednisone 1-2g/day IV)-**inpatient**
  - Then 60-100mg prednisone daily by mouth—may be for 2+ years!
  - *Need to keep ESR down*

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WHAT'S THE TROUBLE WITH LONG-TERM STEROIDS?

- **Significant ocular and systemic side effects**
  - Cataract
  - Elevated blood pressure
  - Blood glucose dysfunction
  - Gastrointestinal ulceration
  - Fluid retention
  - Weight gain
  - Osteoporosis
  - Neuropsychiatric effects including changes in mood

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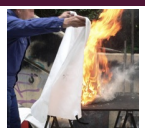
IN MEDICINE, IN GENERAL

- The trend is towards providing 'precision-based medicine'
- Steroids act to suppress the entire immune system
- Biologic agents have a specific therapeutic target in the inflammatory cascade



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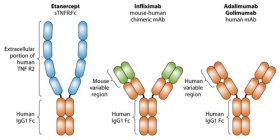
BIOLOGIC AGENTS

- Bioengineered complexes that alter the expression of components of the immune system
- Include monoclonal antibodies
  - Attach to a specific antigen on the surface of an affected cell



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ACTEMRA

- Tocilizumab 162mg/0.9mL
  - Subcutaneous injection (or intravenous infusion)
  - Weekly injection + steroid taper
- Reduces steroid load in GCA treatment
  - Also approved for RA, JIA, cytokine release syndrome

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A LITTLE LESS NEW: HUMIRA

- Adalimumab
- Subcutaneous injection
  - 80mg loading dose
  - 40mg subcutaneous injection every 2 weeks
- Approximately $6922/carton (2 pens)
- FDA approved June 2016 for the treatment of non-infectious intermediate, posterior, and panuveitis
  - Currently 3 biosimilars available
  - Already 9 FDA approved biosimilars

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BIOSIMILARS

- Analogous to biologics as generic medications are to branded small molecule drugs
- Biologic agents are large molecules (i.e. 150,000 Daltons vs. netarsudil 453 Da)
  - 3D structure is complex!
  - Produced from living molecules
- Goal is to be a lower-cost alternative (usually 15-30% of originator biologic)
  - But—manufacturing process is more complicated than for generic medications
  - Drugs need to be prescribed (cannot be substituted)—requires marketing to physicians

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ADVERSE EFFECTS OF TNF ALPHA INHIBITORS

- Unmasking or induction of multiple sclerosis
  - Intermediate uveitis is associated with development of MS
- Reactivation of viral hepatitis, tuberculosis
- "Lupus-like syndrome"
  - Autoantibody formation
- Possible increased risk of lymphoma
  - Medical vs. systemic disease?

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NEW OCULAR STEROIDS

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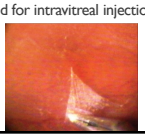
NOT-NEW: INJECTABLE STEROIDS

- Triamcinolone acetonide
  - Kenalog (periocular—sub-Tenon's or subconjunctival)
    - Off-label for intraocular injection
  - Triesence-preservative-free Kenalog
    - Used for intravitreal injection



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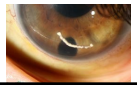
INJECTABLE STEROIDS

- Intravitreal implants-provide sustained release of steroid
  - Ozurdex (dexamethasone 0.7mg) 3-6 months
  - Retisert (fluocinolone acetonide 0.59mg)
  - Iluvien (fluocinolone 0.19mg)—off-label for posterior uveitis-up to 3 years!
  - Yutiq (fluocinolone 0.18mg)—indicated for treatment of non-infectious posterior uveitis-3 years
- Dexamethasone **intraocular** suspension 9% (Dexycu)
  - 5uL dose at the conclusion of cataract surgery



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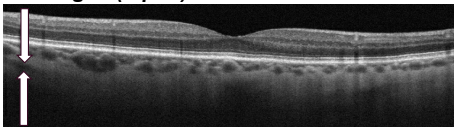
Retinal Disease

Alternative routes of drug delivery

Suprachoroidal space

J code received June 21, 2022

Triamcinolone acetonide injectable suspension 40mg/ml (Xipere)



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OTHER "NEW" STEROIDS

- Loteprednol etabonate suspension 1% (**Inveltys**)
  - Proprietary mucus penetrating particle technology to increase drug delivery
  - BID for post surgical dosing
- Loteprednol etabonate suspension 0.25% (**Eysuvis**)
  - Approved October 27, 2020
  - Short-term (up to two weeks) for the signs and symptoms of dry eye disease. QID
    - Ocular discomfort severity scale 0-100 (improvement from about 70-58 after 2 weeks). Improved about 9 points with vehicle
    - Improvement in conjunctival hyperemia (CCLRU scale)

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LOTEMAX SM

- Loteprednol etabonate ophthalmic gel 0.38%
- SubMicron Technology
  - Greater anterior chamber penetration
  - Faster drug dissolution

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Bottle Design and Drop Size

Plant-derived eye drop bottle

Sugarcane-derived material

Many droppers release upwards of 30µL per drop-also depends how you hold the drop!

Manufacturers tend to overfill bottles

Significant variation

Nanodropper

RESEARCH ARTICLE Open Access

An objective assessment of the variability in number of drops per bottle of glaucoma medication

Daniel B. Moore[1*], Judy Beck[1] and Richard J Kryscio[2]

BMC Ophthalmology

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IOP LOWERING AGENTS

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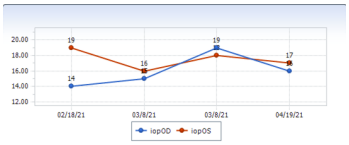
56 YEAR OLD AFRICAN AMERICAN FEMALE

- 56 year old African American female referred for evaluation due to suspicion of glaucoma secondary to optic disc appearance
  - No family history of glaucoma
  - No systemic diagnoses; no systemic medications



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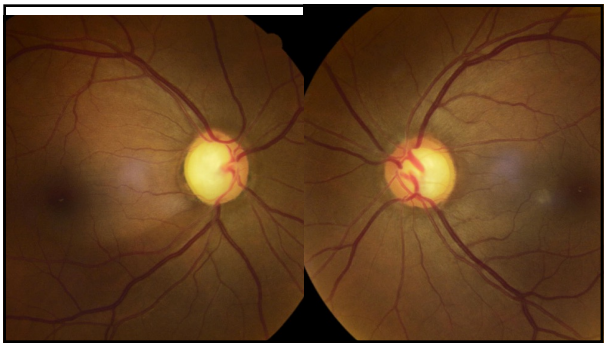

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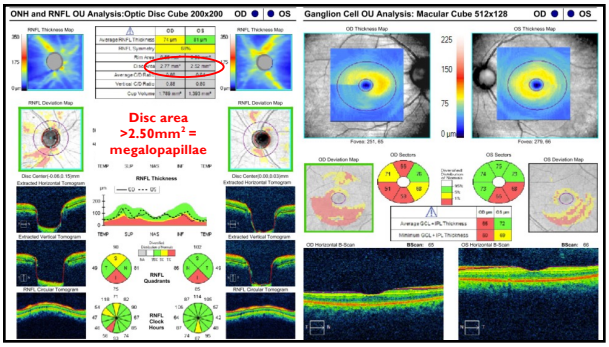

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Angles
OD: 4+Nasal: 4+
OS: 4+Temp: 4+

Gonio Examination:

OD
Superior: OD SUP: open to CBB
Nasal: OD NAS: open to CBB
Temporal: OD Temp: open to CBB
Inferior: OD INF: open to CBB

OS
Superior: OS SUP: open to posterior TM
Nasal: OS NAS: open to CBB
Temporal: OS TEMP: open to CBB
Inferior: OS INF: open to CBB

Comment: OD: iris processes temporal
(-) NVA/AR/PAS 360 degrees OD and OS
tr to 1+ TM pigment OD and OS
Flat iris approach OD and OS

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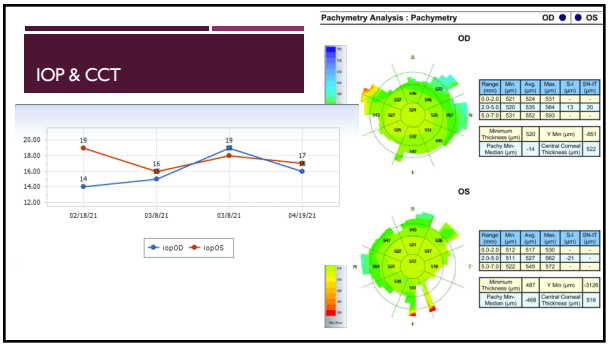
IOP & CCT



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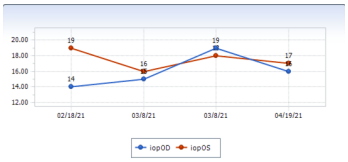
MANAGEMENT

- **1) Medication(s)?**
  - **Topical & oral**
- **2) Laser?**
- **3) Surgical options?**



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IOP LOWERING MEDICATION OPTIONS

- First line treatment:
  - Prostaglandin analog
    - Best adherence at FDA approved dosing
- What does 'maximum medical therapy' mean?
  - ***Classically***:
    - 1) Prostaglandin analog
    - 2-4) CAI
      - Alpha-2 agonist
      - Beta blocker
    - Rho kinase inhibitor
    - ?Pilocarpine

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"NEW" PROSTAGLANDINS

- Latanoprostene bunod 0.024% (Vyzulta)
  - Latanoprost acid + butanediol mononitrate
    - Butanediol monohydrate releases NO which increases outflow through the trabecular meshwork and Schlemm's canal
      - Relaxes trabecular beams
- Latanoprost 0.005% preservative free (Iyuzeh)
- Latanoprost ophthalmic emulsion 0.005% (Xelpros)
  - BAK-free—uses a different preservative: potassium sorbate 0.47%
    - BAK can decrease goblet cell density
  - *Not available from pharmacies*
  - *Uses a "direct pay" method*

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DIRECT PAY EXAMPLE

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RHO KINASE

- Rho kinase family includes proteins which regulate cell shape, motility, proliferation, and apoptosis
  - **Regulate smooth muscle contraction in the trabecular meshwork and ciliary body**
- *May also affect ocular blood blow and retinal ganglion cell survival*
  - *Role in cardiovascular procedures, corneal procedures*
  - *Role in development of fibrosis*

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RHO KINASE INHIBITOR/NOREPINEPHRINE TRANSPORT INHIBITOR

- **Increase trabecular outflow**
- **Lower episcleral venous pressure**
- Netarsudil 0.02% (Rhopressa)
  - QHS
- Netarsudil/latanoprost 0.02%/0.005% (Rocklatan)
  - QHS
- ***Hyperemia-most common effect***
  - Typically improves over time
  - *When do you see your patients back after altering medical therapy?*
- Subconjunctival hemorrhage
- Less common-corneal verticillata
  - Level of the epithelium

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Latanoprost Drops

MD: **JESSICA STEEN OD**
3200 S UNIVERSITY DR
DAVIE, FL 33328

Express Scripts manages the prescription drug benefit for your patient at the request of their plan sponsor. Your patient's prescription benefit requires that we review certain requests for coverage with the prescriber. You have prescribed a medication for your patient that requires Prior Authorization before benefit coverage or coverage of additional quantities can be provided. Please complete the following questions then fax this form to the toll free number listed below. Upon receipt of the completed form, prescription benefit coverage will be determined based on the plan's rules.

SECTION A — Please answer the following questions *(Please fill in the entire circle ● which corresponds to your answer for each question)*

1. What is the indication or diagnosis?
   - ○ Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Note: Open-angle glaucoma includes normal-tension glaucoma, which is also referred to as low-tension glaucoma or normal-pressure glaucoma.
   - ○ Cosmetic conditions (for example, eyelash growth)
   - ○ All other indications or diagnoses

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PATIENT:
Name:
DOB:
Address:
Phone:

PRESCRIPTION INFORMATION:
Rx #:
Drug:
ROCKLATAN 0.02%-0.005% EYE DRP
Sig:
INSTILL 1 DROP INTO BOTH EYES EVERY DAY IN THE EVENING
Quantity: 2.5
Date Written: 06-21-2022

REASON FOR REQUEST:
ALTERNATIVE REQUESTED

PHARMACY COMMENTS:
ALTERNATIVE REQUESTED NOT COVERED

Thank you in advance for taking the time to review this information.
Sincerely,
Your local Pharmacist

SUGGESTED ALTERNATIVES:

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WHERE DO RHOPRESSA & ROCKLATAN FIT IN?

- Efficacy is similar to timolol 0.5% (BID)
  - **In clinical trials
- Ideally a second line treatment
  - Seems to work better with low/moderate IOP (<25mmHg)
- Advantage of once daily dosing vs. other typical second line medication
- Cost?

60

OMIDENEPAG ISOPROPYL 0.002% (OMLONTI)

- Prostanoid EP2 receptor agonist
- Increased uveoscleral and trabecular outflow
- Dosed once daily in the evening
- Does not inhibit adipose tissue formation, does not promote eyelash growth; but theoretically can cause pigmentation increase (although unlikely)
- *Hyperemia, macular edema (possible in pseudophakic and aphakic eyes)*
- *As of November 18, 2021: Complete response letter from the FDA identified deficiencies at contracted manufacturing sites*
  - *June 10, 2022 FDA accepted the resubmitted NDA-PDUFA date November 6, 2022-**approved September 23, 2022***

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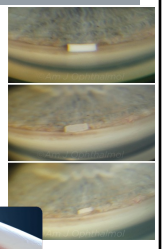
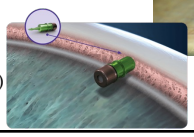
Sustained release devices

Bimatoprost implant 10mcg (Durysta)

Sustained release bimatoprost
Equivalent to about 2-3 drops
Drug release complete in 3-4 months
Lasts about 6 months (may be longer)…extension of the ARTEMIS trial

Implant on day 1, week 16, week 32
Eyelash growth, redness, iris color change?





Travoprost titanium implant (iDose TR)
NDA Submitted to the FDA
Not refillable

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ANTERIOR SEGMENT MEDICATIONS

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Mydriasis

Microdose tropicamide and phenylephrine 1%/2.5%

<1% of patients reported stinging

Utilizes Optejet device (6-8μL of drug)

MIST-1 and MIST-2

FDA approved
May 8, 2023

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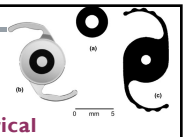
Presbyopia



Small aperture = reduced spherical aberration, increased depth of focus

Pilocarpine 1.25% ophthalmic solution (Vuity)
FDA approved October 30, 2021

Currently under investigation:
Phenotolamine 0.75%**alpha adrenergic antagonist (reversal of pharmacological dilation)
Phentolamine 0.75% + pilocarpine 0.4%
Brimonidine + carbachol
Pilocarpine
Pilocarpine 0.302% + phenylephrine 0.624% + pheniramine 0.0772%

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Reversal of Mydriasis

Preservative-free phentolamine 0.75% (Nyxol)

Nonselective alpha 1 and 2 blocker

Currently the molecule is FDA approved for pheochromocytoma and reversal of oral anesthesia

PDUFA Date
September 28, 2023

MIRA-1, 2, 3, 4

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Anterior Segment

Dry Eye Disease

Varenicline solution nasal spray 0.03mg

Activates the trigeminal parasympathetic pathway = increased production of basal tear film

FDA approved October 18, 2021

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TYRVAYA (VARENICLINE SOLUTION NASAL SPRAY 0.03MG)

- One spray in each nostril twice daily
- Most common adverse reaction:
  - **Sneezing** (82%) of patients
  - *Cough, throat irritation, nose irritation*

75

Anterior Segment

Vevye (CyclASol 0.1% cyclosporine A in EyeSol)

EyeSol = water-free technology that increases surface contact time

ESSENCE1 & ESSENCE2

FDA approved June 9, 2023

Twice daily dosing; multidose; smaller drop size

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Anterior Segment

Dry eye disease associated with meibomian gland dysfunction

Meibo (100% perfluorohexyloctane [F_6H_8])

Prevents evaporation and stabilizes the tear film

FDA Approved May 18, 2023

SEECASE, GOBI, MOJAVE

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Anterior Segment

Demodex blepharitis

Lotilaner ophthalmic solution 0.25% (TP-03)

Demodex is more common than we think

Antiparasitic agent

PDUFA Date August 25, 2023

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Anterior Segment

Dry eye disease, allergic conjunctivitis

Reproxalap

RASP modulator-reduces inflammation through reduction of cytokine release and inflammasome activity

PDUFA Date November 23, 2023

TRANQUILITY & TRANQUILITY2

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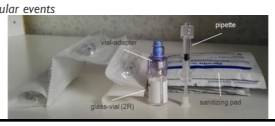
OXERVATE

- Cenegermin 0.002% (20mcg/mL)
  - Recombinant human nerve growth factor
- FDA approved August, 2019 for the treatment of neurotrophic keratitis
- 6x daily for 8 weeks
- *What do you think the most common adverse effect was in the pivotal trial?*
  - *39.1% reported ocular events*



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THYROID EYE DISEASE

- What types of thyroid disease are most likely to cause Graves disease?
- **Autoimmune thyroid disease**
- Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → activate T lymphocytes → activate orbital **fibroblasts** → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

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TEPROTUMUMAB (TEPEZZA)

- Monoclonal antibody
  - Targets insulin like growth factor 1-binds to IGF-1R and blocks its activation
  - Fibroblasts often have IGR-1R
    - Autoantibodies have no binding site!
- Intravenous infusion-series of 8 treatments over 24 weeks
  - Every 3 weeks

Autoantibody and autoantigen formation in the orbit leads to production of cytokines (proinflammatory) → **activate T lymphocytes** → activate orbital fibroblasts → proliferate hyaluronan which leads to soft tissue expansion = thyroid eye disease

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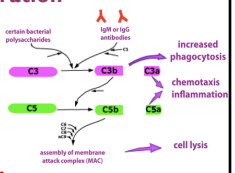
Retinal Disease

Dry age-related macular degeneration

CFH polymorphism increases risk of AMD (complement control protein)

Components of drusen and oxidative stress can trigger complement cascade → apoptosis



Complement over-activation is implicated in pathogenesis of AMD

Classical, alternative, lectin pathways converge to activate C3 C5 activation can lead to increased VEGF expression by the RPE

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COMPLEMENT INHIBITORS IN GA

APPROVED February 17, 2023

- ***Geographic atrophy doesn't get better-the goal is to slow progression***
- APL-2 (Pegcetacoplan)-C3 inhibitor
- Met phase 2 endpoints (FILLY) in September 2019-slows GA rate of progression **in a dose-dependent manner**
- Phase 3 trials (DERBY & OAKS)
  - Endpoints met in OAKS, very close in DERBY
  - Pooled data met endpoints
- **Slows the growth rate of geographic atrophy**
- *Fast track designation from FDA (GA)-Unmet clinical need*
- ***Whatever drives a druse towards GA is the same mechanism that seems to cause GA expansion***

Empaveli-paroxysmal nocturnal hemoglobinuria approved in 2021

85

Pegcetacoplan (Syfovre)

Interesting safety signal: increased risk of exudation
Cumulative data: 12.2% in monthly, 6.7% EOM, 3.1% sham

At month 24, combined data: reduction vs. sham from baseline:
21% (monthly dosing)
17% (every other month dosing)

Nonsubfoveal subgroup had even greater reduction vs. sham

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Avacincaptad Pegol (Zimura)

GATHER1 (Phase 2b/3)-endpoints met
GATHER2 (Phase 3)-primary endpoint met

Interesting: slowed iRORA to cRORA change—and drusen to iRORA

Treatment effect based on geographic location was identified

Safety signal: CNV rate 9.0% in GATHER1 and 6.7% in GATHER2

PDUFA Date
August 19, 2023

Expect that if an efficacy signal was identified at month 12, the difference between groups should continue to increase at months 18 and 24

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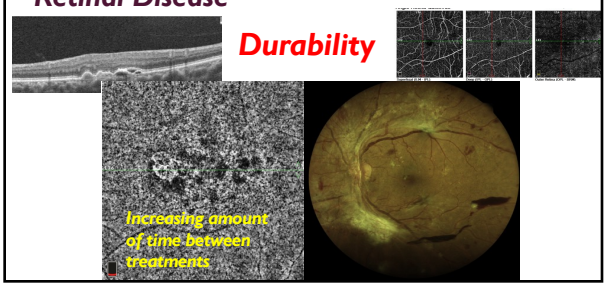
Retinal Disease



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Retinal Disease

Neovascular AMD
(and diabetic eye disease…more generally, retinal vascular disease)

Extracellular VEGF pathways
VEGF-A
VEGF-B
VEGF-C
VEGF-D
PlGF

TKI pathways

TIE2 activation pathways

Integrin pathways

Gene therapy

Unmet needs in management of retinal disease?

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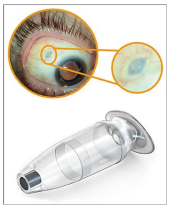
PORT DELIVERY SYSTEM WITH RANIBIZUMAB

As of July 1, 2022-permanent J-code

- Permanent, reusable, surgically-'placed' reservoir
- 3.5mm pars plana incision
- Holds 20 µL of custom formulation of ranibizumab
  - Phase 2: LADDER → PORTAL
  - Phase 3: ARCHWAY
    - Refill every 6 months
    - Met primary endpoints
      - 10.7 injections in ranibizumab arm vs. 2 fills
- October 18, 2022: voluntary recall



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Port Delivery System in Patients with DME

PAGODA Trial

Q24 week refill exchange

Primary endpoints met

No endophthalmitis or retinal detachment through 64 weeks

Risks seem to be less than in nAMD patients

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High Dose Aflibercept (8mg)

PHOTON (DME) and PULSAR (nAMD)

12 and 16 week dosing regimens vs. Eylea x q8weeks

93% (PHOTON) and 83% (PULSAR) maintained q12 weeks or greater

PDUFA Date
June 27, 2023

Accepted for priority review

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ADVERSE EFFECTS OF ANTI-VEGF INJECTIONS

- Subconjunctival hemorrhage
- Increased intravitreal volume
  - Increased intraocular pressure
    - Acutely—and long term
- Risk of endophthalmitis
  - Approximately 1/2659 injections
    - Role of topical antibiotic prophylaxis?
- Risk of retinal detachment, vitreous hemorrhage
- Stroke, myocardial infarction-conflicting data

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BEOVU

- Brolucizumab (Beovu)-approved October 8,2019
  - Single chain antibody fragment inhibitor of VEGF
  - Molecular weight half of ranibizumab
    - Smaller molecule = improved penetration, faster clearance, lower systemic exposure
  - Phase 3 trials-top line results
    - HAWK/HARRIER trials showed non-inferiority to Eylea in visual acuity and fluid reduction in patients with wet AMD
    - Improved acuity vs. aflibercept
    - Improved central thickness and fluid on OCT vs. aflibercept
  - **12 week duration (after 3 monthly loading doses) for nAMD**
  - **On label for neovascular AMD;** *KITE and KESTREL (DME) in progress,* ~~*RAPTOR and RAVEN & MERLIN*~~

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BEOVU

- February, 2020: 14 cases of vasculitis (11 were occlusive retinal vasculitis)
  - As of March 13, 2020: more than 65,000 injections
- Through June 26, 2020
  - 7.92 events/10,000 injections (retinal vasculitis, retinal vascular occlusion-or both)
    - As high as 4% incidence of inflammation; and 0.7% of 101 and loss of 15+ letters
- *Contraindicated in patients with active intraocular inflammation*
  - *But…so is Eylea*

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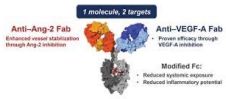
FARICIMAB (VABYSMO)

Permanent J-code as of October 1, 2022



- FDA approved January 28, 2022-the newest! **(currently)
- Bispecific antibody
  - Targets angiopoietin-2 (Ang-2) and VEGF-A
    - Ang-2 and VEGF work in concert-increases permeability and inflammation
- TENAYA and LUCERNE (nAMD)
  - Vs. aflibercept
  - Treated every 3-4 months (after 4 monthly doses)
    - 80% of individuals were able to go 3+ months between treatments in the first year
  - YOSEMITE and RHINE (DME)

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What We've Learned

VEGF starts to increase 6-8 weeks after injection of faricimab

Ang2 suppression lasts about 12 weeks

Aflibercept does not suppress Ang2

Seems to be a true synergistic effect between VEGF & Ang2

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Is faricimab the new "gold standard"?

FDA draft guidance (February 2023) for the development of new drugs for the treatment of neovascular AMD

Noninferiority to ranibizumab or aflibercept…

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COST EFFECTIVENESS OF ANTI-VEGF

- $2190 faricimab (6mg/0.05mL)-Vabysmo
- $1850 brolucizumab (6mg/0.05mL)-Beovu
- $1850 aflibercept (2.0mg/0.05mL)-Eylea
- $1170 ranibizumab (0.3mg/0.05mL)-Lucentis
- $60 bevacizumab (1.25mg/0.05mL)-Avastin

- **Bevacizumab is a typically the first line anti-VEGF in the USA**

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WHILE WE'RE SPEAKING ABOUT BEVACIZUMAB

- Bevacizumab-vikg (Lytenava)
  - BLA submitted March 31, 2022
  - Anticipated approval late 2022 or first quarter 2023
- NORSE 2-superiority trial
  - 113 patients received 12 bevacizumab-vikg (monthly)
  - 115 patients received 5 ranibizumab injections

  1, 2, 3, 6, 9)-based on PIER (2008) dosing regiment from the package label
- ***Who did better?***

----------DOSAGE AND ADMINISTRATION----------
For Ophthalmic Intravitreal Injection Only (2.1)

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (2.2)
LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the nine months after 3 initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly.

Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly.

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RETINAL BIOSIMILARS

- **The first:**
- Ranibizumab-nuna (Byooviz) FDA approved September 17, 2021
  - nAMD, macular edema following RVO, and myopic choroidal neovascularization
  - Launch July 2022-list price $1130/vial
- **The most recent:**
  - *Interchangeable biosimilar to Lucentis:* ranibizumab-eqrn (Cimerli)
    - *Launched! List price: $1360 for 0.5mg dose*

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Anti-VEGF in DME & DR

DRCRnet Protocol S (2016): Ranibizumab (Lucentis) in non-inferior to PDR

Protocol T (2018) Aflibercept vs. bevacizumab vs. ranibizumab in DME: For VA 20/50 or worse, aflibercept better at improving VA

Protocol V (2019): Center-involved DME (20/25+) no difference in vision at 2 years

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Anything other than intravitreal injections?

APX3330 oral tablet for the management of diabetic retinopathy

ZETA-1 Phase 2b trial
Targets apurinic/apyrimidinic endonuclease 1/redox effector factor-1 (APE1/Ref-1) protein = reduction of abnormal new vessel formation (reduces VEGF & VEGF signaling) & inflammation (reduces TNF alpha)

OTT166
DREAM Phase 2 trial
Integrin inhibitor—TOPICAL

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OPTIC & LUNA TRIALS (IXOBEROGENE SOROPARVOVEC) IXO-VEC

- September 2018-FDA awarded fast track designation to a gene therapy for exudative AMD
- Aflibercept coding sequence + adenoviral associated vector (ADVM-022)
  - 30 patients
- Coding sequence (cDNA) injected intravitreally
  - Replicates in deep retina producing detectable 'aflibercept' protein in vitreous, deep retina, and choroid
- May last up to 2 years
- Durability up to 92 weeks (cohort 1-high dose)
  - High dose vs. low dose; 13 day oral steroid vs. 6 week topical ophthalmic steroid
- ***Phase 2 underway!***

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BOTTOM LINE

- Therapeutic innovations in eye care are changing the way ocular disease is managed
  - Treatment targets and treatment modalities are rapidly evolving
- Ensuring access to the most effective medications in a particular clinical circumstance begins with understanding available options
- The role of regulatory powers, including the FDA is continuing to adapt to environmental circumstances

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BOTTOM LINE

- Further developments aim to:
  - Identify new treatment targets
  - Reformulate existing agents
  - Develop alternative routes of administration
  - Increase the amount of time between treatments
  - Reduce cost of treatment
  - Improve patient quality of life

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THANK YOU!

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