Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update with New Drug Evaluation: Glaucoma Drugs

Date of Review: May 2018

Generic Name: latanoprostene bunod
Generic Name: netarsudil dimesylate

Date of Last Review: January 2015
End Date of Literature Search: 02/26/2018
Brand Name (Manufacturer): Vyzulta (Bausch & Lomb, Inc)
Brand Name (Manufacturer): Rhopressa (Aerie Pharmaceuticals, Inc)
Dossier Received: yes – Vyzulta / no - Rhopressa

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
This class update was prompted by the approval of two new treatments for glaucoma, latanoprostene bunod (LB) and netarsudil. The evidence used for these approvals will be evaluated in addition to any new comparative evidence published for glaucoma therapies since the last review.

Research Questions:
1. Are there comparative efficacy differences between glaucoma treatments based on outcomes such as intraocular pressure (IOP), loss of vison, or blindness?
2. Are there differences in harms between treatments for glaucoma that would have a clinical impact on patient care and should be factored into treatment decisions?
3. Are there subgroups of patients in which LB, netarsudil or other glaucoma treatments are safer or more effective than other available ophthalmic treatments for glaucoma?

Conclusions:
- No meaningful differences were found after evaluation of the evidence for comparative efficacy differences between treatments for glaucoma. Guidance from National Institute for Health and Care Excellence (NICE) recommends the use of generic prostaglandins first line in adult patients with chronic open angle glaucoma (OAG) or ocular hypertension (OH).[1]
- Canadian Agency for Drugs and Technology in Health (CADTH) studied the comparative efficacy and harms of bimatoprost compared to other prostaglandins.[2] Moderate strength of evidence found combination therapy with bimatoprost to be more effective in lowering IOP than other combinations; however, despite statistically significant differences in some cases the small difference between treatments (up to a maximal difference of 2mmHg) is unlikely to be clinically significant. Monotherapy comparisons of bimatoprost, travoprost and latanoprost demonstrated similar IOP lowering. Bimatoprost, used as monotherapy or combination therapy, was associated with the highest incidence of hyperemia. Latanoprost was found to have the most benefit with least risk of harms amongst the comparisons.

Author: Kathy Sentena, PharmD

- *Latanoprostene*: There was low strength of evidence of IOP lowering of 7-9 mmHg in patients treated with LB compared to 6-8 mmHg in patients treated with timolol, with OAG or OH diagnosis, based on two poor quality, noninferiority studies.[3,4]
- *Netarsudil*: There was low strength of evidence of IOP lowering in patients treated with netarsudil based on two poor quality, noninferiority studies in patients with OAG and OH.[5] IOP decreases from baseline ranged from 3.3 to 5.0 mmHg in the netarsudil once daily group (approved dose), 4.1 to 5.4 mmHg in the netarsudil twice daily group and 3.7 to 5.1 mmHg in the timolol group.
- Hyperemia was more common with LB and netarsudil compared to timolol. LB was associated with up to an 8% higher incidence of hyperemia than timolol and netarsudil was associated with up to a 45% higher incidence compared to timolol.[3–5]

Recommendations:
- No changes to the PDL for glaucoma drugs are recommended based on efficacy or safety data.
- No PDL changes recommended after evaluation of comparative drug costs in executive session.

Current Policy:
- The Oregon Health Plan (OHP) provides coverage for glaucoma with the current policy preferring treatments from each class of treatments; miotics, alpha-adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues. Previous reviews, including the last update in January of 2015, have not found meaningful differences in efficacy/effectiveness within drug classes of ophthalmic medications used to treat glaucoma. Cost effectiveness and differences in harms data have been the driving forces for preferring specific therapies (**Appendix 1**). Newer fixed-combination products have not shown to provide substantial clinical benefit over the use of individual components. There are currently no prior authorization criteria for this class; however, utilization of PDL agents is high. There are approximately 3,000 Oregon Health Plan (OHP) fee-for-service patients with a diagnosis of glaucoma with a minimal impact on overall OHP healthcare costs.

Background:
Glaucoma is the second leading cause of blindness in the world.[6] Glaucoma is characterized by two variations: OAG and angle-closure glaucoma. A 2016 guideline estimates the incidence of OAG to be 2.2 million people in the United States, representing a 2% prevalence in adults.[7] The suggested incidence of angle-closure glaucoma is 20 million people worldwide.[8] Open-angle glaucoma is more common in individuals of European and African decent and the incidence of angle-closure glaucoma is higher in people of Asian heritage. Risk factors for the development of open-angle glaucoma include: age, black race, family history, and elevated IOP. Hypertension and diabetes have also been associated with an increased risk of OAG. Risk factors for development of visual loss and progression to blindness are not fully known.[6] Risk factors for patients with angle-closure glaucoma are family history, age over 60 years, female, hyperopia (farsightedness), certain medications, race and pseudoexfoliation.

Open-angle glaucoma causes peripheral visual field loss due to optic neuropathy. Open-angle glaucoma is often associated with elevated IOP levels and reduction in IOP is important to prevent the progression to loss of vision.[1] Elevated IOP is the result of increased aqueous production or decreased aqueous outflow. The increased pressure can result in “cupping” of the optic nerve causing loss of ganglion cell axons. The pathogenesis of OAG is not clear but thought to be a combination of circulatory or extracellular matrix factors, variation in axon susceptibility and systemic factors. If left untreated OAG can cause visual field loss and irreversible blindness.[6] Angle-closure glaucoma is the result of narrowing or closure of the anterior chamber angle. This chamber is responsible for drainage of the aqueous humor, which is the fluid that fills the eyeball. Prevention of drainage from this pathway can cause increased IOP with subsequent damage to the optic nerve. Angle-closure glaucoma is caused by certain anatomical traits of the eye. Acute blockage of the entire angle in angle-closure glaucoma can cause rapidly rising IOP and subsequent vision loss and potential blindness if not treated. Chronic angle-closure glaucoma can occur over time and

result in scarring of the optic nerve.[6] Secondary glaucoma can be caused by uveitis, trauma, glucocorticoids, vasoproliferative retinopathy, or ocular syndromes (i.e., pigment dispersion or pseudoexfoliation).

The consensus for initiating treatment in patients with open-angle glaucoma are 2 IOP readings of more than 22 mmHg, with normal ranges of IOP being 8-21 mmHg.[6] Treatment options for lowering IOP include medications, laser or surgery; however, pharmacotherapy or laser are preferred. If medical treatment is used, prostaglandins (e.g., latanoprost, travoprost, bimatoprost) are recommended as the first-line based on once-daily dosing, improved efficacy and low incidence of side-effects compared to beta-blockers (e.g., betaxolol, carteolol, timolol), carbonic anhydrase inhibitors (e.g., brinzolamide, dorzolamide), and alpha adrenergic agonists (e.g., brimonidine, apraclonidine).[1] Beta-blockers are commonly used as a second-line treatment option due to side effects such as bradycardia, worsening heart failure and increased airway resistance. Alpha adrenergic agonists have been shown to have similar efficacy to beta-blockers in lowering IOP but a higher incidence of ocular side effects prevents it from being an initial treatment option. Topical carbonic anhydrase inhibitors have been shown to be less effective than other options and associated with burning, stinging and allergy.[1] Miotics (e.g., pilocarpine) are associated with fixed, small pupils, myopia, and increased visual disturbances and are therefore not widely used. If monotherapy is not effective, combination therapy of beta blockers plus prostaglandin or beta blocker plus carbonic anhydrase inhibitor have been shown to lower IOP more than single therapy. Fixed-dose combination products are offered most commonly with timolol and an additional agent.[1]

Acute treatment of angle-closure glaucoma includes methods to lower quickly reduce IOP.[6] A regimen of topical ophthalmic drops consisting of a beta-blocker, an alpha agonist and treatment to produce miosis (i.e., pilocarpine) is often recommended. Systemic treatment with acetazolamide, mannitol or oral glycerol or isosorbide is also recommended. Once IOP is reduced, laser peripheral iridotomy is used to prevent future elevations of IOP. Peripheral iridotomy is the treatment of choice for patients with angle-closure glaucoma. Secondary angle-closure glaucoma is treated with removing the offending cause if possible and utilizing medications recommended for open-angle glaucoma if necessary.

Outcomes used to track response to therapy are IOP, visual field changes, condition of the optic nerve and progression to blindness.[7] The goal of treating open-angle glaucoma is to lower IOP to a level to prevent further eye damage. The magnitude of IOP lowering is dependent upon the degree of optic nerve damage, rate of progression, family history, age or presence of disc hemorrhages.[7] There is no standard IOP target; however, IOP lowering of 25-30% (approximately 6-7 mmHg) below IOP at presentation has been suggested.[6,7] Evidence has shown that lowering IOP slows progression of visual impairment associated with elevated IOP levels.

For the glaucoma class of medication there is approximately 95% preferred drug utilization within the fee-for-service population. As expected, the highest utilization is within the prostaglandin class followed by alpha-2 agonists.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched

for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

CADTH – Prostaglandins for Ophthalmic Use: Rapid Response Report

CADTH completed a systematic review of the evidence on prostaglandin use in adult patients with glaucoma in July 2015.[2] The focus of the review was on the comparative efficacy and harms of bimatoprost compared to other ocular prostaglandins (latanoprost, tafluprost, or travoprost). Eighteen publications were considered in the review which included systematic reviews and randomized controlled trials. The mean ages reported in the identified literature were 46 to 68 years and 37% to 64% were females.

One systematic review of 7 adequate quality trials compared fixed combinations of bimatoprost and timolol (B/T) to travoprost and timolol (TR/T) or latanoprost and timolol (L/T) in patients with glaucoma.[2] Diurnal IOP reduction difference favored bimatoprost combinations; -1.94 mmHg (95% confidence interval [CI], 0.19 to 3.68) for B/T compared to TR/T and -0.88 (95% CI, 0.42 to 1.33) for B/T compared to L/T ($p<0.05$ for both comparisons). The incidence of conjunctival hyperemia was higher in both groups of patients treated with B/T compared to TR/T or L/T, with odds ratios [OR] of 1.65 (95% CI, 0.48 to 5.70) and 1.85 (95% CI, 1.09 to 3.13), respectively.[2]

A 2012 Agency for Healthcare Research and Quality (AHRQ) systematic review was included in the CADTH rapid response report. Fair to moderate quality evidence, found more IOP lowering with bimatoprost compared with travoprost (RR 1.19; 95% CI, 1.00 to 1.42).[2] Weighted mean differences were statistically significant in favor of bimatoprost for time periods 8 am and 12 pm, 1.02 mmHg (95% CI, 0.32 to 1.72) and 0.86 mmHg (95% CI, 0.12 to 1.59). A meta-analysis found bimatoprost to lower IOP more than latanoprost (RR 1.70; 95% CI, 1.44 to 2.02). The weighted mean difference between the groups ranged from 0.50 to 1.17 mmHg ($p<0.05$ at all time periods) in favor of more IOP lowering with bimatoprost.[2] The small differences in IOP lowering demonstrated in this systematic review are unlikely to be clinically meaningful. Hyperemia was more common with bimatoprost compared to other treatments in both comparisons. There were no meaningful differences between the prostaglandins studied in the incidence of ocular irritation, inflammation, cystoid macular edema and iris pigmentation.

Monotherapy Active Treatment Comparisons

Six randomized, fair to good quality, monotherapy trials compared bimatoprost, travoprost and latanoprost.[2] Intraocular pressure reduction was the primary outcome in all the studies. Most of the studies found small differences in IOP reduction between groups; however, one study found bimatoprost to statistically significantly lower IOP compared to travoprost and latanoprost with reductions at 12 weeks of 8.8 mmHg, 7.6 mmHg and 7.3 mmHg, respectively. Small differences in IOP lowering are of unknown clinical significance.[2] Four randomized controlled trials comparing bimatoprost to travoprost found no difference in one study, travoprost to be noninferior to bimatoprost in one study and in two studies bimatoprost was found to be superior to travoprost. The incidence of hyperemia was found to be similar between bimatoprost, travoprost and latanoprost in three of the randomized controlled trials. The other two trials that reported on hyperemia found a higher incidence with bimatoprost compared to travoprost and latanoprost; however, statistical significance was not reported.

Monotherapy Bimatoprost and Travoprost Treatment Comparisons

Bimatoprost was compared to travoprost in four, fair quality randomized-controlled trials. Two trials found bimatoprost to lower IOP more than travoprost, 7% more in one trial and by 0.7 mmHg in another ($p<0.05$ for both comparisons).[2] One study found a travoprost to be non-inferior to bimatoprost and a second study found no difference between treatments. Hyperemia was more common in patients using bimatoprost but the numerical results were not reported.

Combination Therapy Comparison

One good quality randomized controlled trial found the combination of bimatoprost and timolol to be similar in lowering IOP compared to travoprost and timolol.[2] A randomized controlled trial which compared bimatoprost, latanoprost and travoprost (all in combination with timolol) found similar IOP values at 3-months to be 12.10 mmHg, 11.59 mmHg and 14.00 mmHg, respectively ($p=0.0$ for all comparisons). The incidence of hyperemia was 23.8% with bimatoprost + timolol compared to 10% with travoprost + timolol (p-value not provided).[2]

New Guidelines:

NICE – Glaucoma: Diagnosis and Management

In 2017 NICE issued guidance on the management of chronic OAG and OH in adults ages 18 and older.[1] Assessment, diagnosis and treatment strategies were presented. Strategies for the treatment of angle closure glaucoma were not included in this review. Evidence was evaluated using the GRADE technique. Effectiveness of prostaglandins and beta-blockers were analyzed via a network meta-analysis, which is low quality evidence. For the purposes of this review, only the pharmacological treatment recommendations are provided.

2017 NICE recommendations for the treatment of OH:[1]

1. Generic prostaglandin analogs are recommended for patients with an IOP of 24 mmHg or more if they are at risk of visual impairment within their lifetime.
2. Treatment should not be offered to patients who are not at risk of visual impairment within their lifetime.
3. Patients who cannot tolerate their current treatment should be offered a different pharmacological option if IOP is 24 mmHg or higher. An alternative generic prostaglandin is recommended first line and a beta-blocker should be considered if prostaglandins are not tolerated. If neither of the previous options are tolerated then the following should be considered: non-generic prostaglandin, carbonic anhydrase inhibitor, sympathomimetic, miotics or combination of treatments.
4. In patients with an IOP of 24 mmHg or greater whose current treatment is failing to reduce IOP to a sufficient level, recommend a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to prevent risk of sight loss. Reduction of IOP may require topical treatments from different therapeutic classes.
5. Patients who have elevated IOP despite pharmacologic therapy should be referred to an ophthalmologist to discuss other treatment options.
6. Preservative-free eye drops should be used in patients with an allergy to preservatives and clinically significant and symptomatic ocular surface disease if they are high risk of conversion to chronic OAG.

2017 NICE recommendations for suspected chronic OAG:[1]

1. Patients with IOP less than 24 mmHg and suspected OAG should not receive treatment. Patients with an IOP of 24 mmHg or higher with suspected OAG should be offered a generic prostaglandin.

2017 NICE recommendations for patients with chronic OAG:[1]

1. Generic prostaglandins are recommended first line in patients with chronic OAG.
2. Patients that have advanced OAG should be offered surgery in addition to pharmacotherapy.
3. Patients who present with advanced chronic OAG should be offered a generic prostaglandin while awaiting surgery.
4. A change in pharmacological therapy should be considered in the following circumstances: IOP is not reduced to the extent to prevent the progression to loss of sight, there is progression in optic nerve head damage, there is progression of visual field defect, or drug intolerance.
5. Patients who fail to have successful IOP lowering should be assessed for adherence and proper technique. If adherence and instillation technique is appropriate then one of the following options are recommended: offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or combination therapy with drugs from different therapeutic classes; laser trabeculoplasty; surgery with adjunctive pharmacotherapy.
6. Surgery and pharmacotherapy should be recommended in patients with chronic open angle glaucoma who are at risk of progressing to loss of sight despite pharmacotherapy.
7. Patients who cannot tolerate a drug from one therapeutic class should be offered a drug from a different therapeutic class or preservative-free eye formulation if an allergy is suspected or clinically significant and symptomatic ocular surface disease is suspected
8. Patients who fail treatment from 2 therapeutic classes should be considered for surgery with pharmacotherapy augmentation.
9. Patients who have had surgery but still have elevated IOP may need pharmacotherapy, including multiple drugs from different pharmacological classes.
10. Patients who have chronic OAG who are not candidates for surgery should be offered pharmacological treatment, including treatment from multiple classes if needed. Laser trabeculoplasty or cyclodiode laser treatment may also be an option.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 127 citations were manually reviewed from the initial literature search. After further review, 123 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the evidence tables below.

NEW DRUG EVALUATION: Latanoprostene Bunod
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The clinical efficacy of LB comes from two, randomized, multi-center, phase 3, double-blind, noninferiority studies (**Table 2**). In both studies LB 0.024% once daily was compared to timolol 0.5% twice daily in adult patients with OAG or OH.[3,4] The primary endpoint was the decrease in IOP from baseline at 8AM, 12PM and 4PM at week 2, week 6 and month 3 measured in the intent-to-treat (ITT) population, with missing data imputed using last observation carried forward (LOCF),

for both studies. Noninferiority was determined in the ITT population if the upper limit of the CI for the difference did not exceed 1.5 mmHg at all 9 time points and did not exceed 1.0 mmHg for more than 5 of the 9 time points. Superiority was tested if noninferiority was met. Superiority was achieved if the upper limit of the 95% CI did not exceed 0 mmHg at all 9 time points. Analysis was also performed on the per protocol population to substantiate results.

In the first study (n=417), patients meeting the inclusion criteria (i.e., adult patients with OAG or OH) were a mean age of 64 years, 58% female, predominately European or African ancestry with a mean baseline IOP of 26.6 mmHg.[3] Seventy-two percent of patients had history of prior use of topical IOP-lowering therapy. LB was associated with more IOP lowering compared to timolol at all 9 time points in the ITT study population, with mean IOP values after treatment of 17.8 mmHg to 18.7 mmHg and 19.1 mmHg to 19.8 mmHg, respectively. LB was found to be noninferior to timolol with the upper limit of the 95% CI for the difference between the two treatments being less than 1.0 mmHg for all 9 time points. Since noninferiority was met, superiority was also analyzed and LB was found to be superior to timolol since the upper limit of the 95% CI was less than or equal to 0 mmHg for all 9 time points. Per-protocol results were not given but were stated to support the ITT results. For the secondary endpoint of proportion of patients with an IOP less than 18 mmHg at all 9 time points, 23% of patients treated with LB obtained this endpoint compared to 11% patients treated with timolol (mean difference [MD] 12%; 95% CI, 4.3 to 18.9; p=0.005; ARR 12/NNT 9).[3] Thirty-five percent of patients treated with LB had an IOP reduction greater than 35% from baseline at all 9 time points compared to 20% of patients treated with timolol (MD 15%; 95% CI, 6.6 to 24.0; p=0.001; ARR 15/NNT 7).

The second study was very similar to the first study in methodology and baseline characteristics of included patients (n=387).[4] Patients had moderate levels of IOP elevations (mean baseline IOP 26.6 mmHg), mean age of 65 years and 58% were female. Seventy-two percent of patients had used some type of topical therapy for IOP lowering. Mean IOP levels after treatment for LB ranged from 17.7 to 19.2 mmHg and from 18.8 to 19.6 mmHg for timolol.[4] LB was found to be noninferior to timolol based on the upper limit of the mean difference of the 95% CI not exceeding 1.0 mmHg at any of the 9 time points. LB was not superior to timolol since one of the nine time points exceeded 0 mmHg. Authors stated that per-protocol results were consistent with ITT findings but specific data were not provided.

Limitations to this evidence include the use of an ITT analysis for the primary endpoint in a noninferiority study which can bias the results in direction of no difference between treatments. A more appropriate analysis would be on the per-protocol population which was done but the results were not reported in the published trial. The FDA medical review did contain the per protocol results which do substantiate the ITT findings.[9] The timing of testing may have also influenced the results in favor of LB. The maximal effect of timolol has been shown to be 2 hours post-dose which was not studied in the trials; however, the maximal effect of LB would have been captured at the pre-specified time points.[9] The FDA analysis concluded that there was no clinically significant difference between LB and timolol. Three-month study design prevents long-term conclusions on safety and efficacy. Both of the above studies have open-label extension studies that will help to inform the safety of long-term use.

Clinical Safety:
The number of patients who discontinued LB due to adverse events was 1.4% in both studies compared to 0.7% to 3.0% for placebo.[3,4] The most common adverse reactions seen in 2% or more of patients treated with LB are conjunctival pain, hyperemia, eye irritation, eye pain and instillation pain.[10] LB carries a warning for pigmentation changes to the tissues which may be irreversible in some cases. Increases in length, thickness and number of lashes or hairs have also be seen with LB treatment, as well as other prostaglandin therapy.

Table 1. Pharmacology and Pharmacokinetic Properties.[4,10]

Parameter	
Mechanism of Action	Prostaglandin analog which increases the outflow of aqueous humor through the trabecular meshwork and uveoscleral routes. Latanoprostene is metabolized to latanoprost acid (prostaglandin) and butanediol mononitrate (nitic-oxide donating moiety).
Oral Bioavailability	Not applicable
Distribution and Protein Binding	No distribution studies performed
Elimination	Not provided
Half-Life	Not provided
Metabolism	Liver

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Visual disturbance
2) Blindness
3) Intraocular pressure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Reduction in intraocular pressure from baseline

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Weinreb, et al[3] (Apollo) Phase 3, DB, MC, PG, NI, RCT	1. Latanoprostene Bunod 0.024% once daily at night (L) 2. Timolol 0.5% twice daily (T) 3-month study	Demographics: Mean age: 64 years Female: 58% White: 78% Treatment naïve to topical IOP-lowering therapy: 28% Mean baseline IOP: 26.6 mmHg Key Inclusion Criteria: - OAG or OH in one or both eyes - 18 years of age or older - IOP ≥26 mmHg at a minimum of 1 time point, ≥24 mmHg at a minimum of 1 time point, ≥22 mmHg at 1 time point in the same eye and IOP ≤36 mmHg at all 3	ITT: 1. 284 2. 133 PP: 1. 192 2. 80 Attrition: 1. 92 (32%) 2. 53 (40%)	Primary Endpoint: Mean IOP (mmHg) at 8 AM, 12 AM and 4 PM at weeks 2, 6 and month 3 visits: **Week 2 – 8AM** L: 18.6 T: 19.8 MD -1.2 (95% CI, -0.5 to -1.9) **Week 2 – 12PM** L: 18.0 T: 19.4 MD -1.4 (95% CI, -0.7 to -2.1) **Week 2 – 4PM** L: 18.1 T: 19.2 MD -1.1 (95% CI, -0.5 to -1.8) P<0.001 for all comparisons **Week 6 – 8AM**	 NA NA NA	Discontinuations due to adverse events: L: 4 (1.4%) T: 4 (3.0%) P-value not reported Eye Irritation: L: 11 (3.9%) T: 3 (2.2%) P-value not reported Conjunctival Hyperemia: L: 8 (2.8%) T: 2 (1.5%) P-value not reported	 NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) Randomized 2:1 by an unmasked statistician using SAS software. Performance Bias: (low) Each product was packaged the same to mask treatment assignment. Detection Bias: (unclear) Details of blinding were not provided. Attrition Bias: (high) Very high attrition was seen in both groups. Analysis was done on the ITT population which can bias results in favor of no difference between groups. Reporting Bias: (low) Industry funded study. Outcomes were reported as described.

		measurement time points in both eyes at baseline - BCVA of +0.7 logarithm of the minimum angle of resolution or better in either eye. <u>Key Exclusion Criteria</u>: - Participation in any clinical trial within 30 days - Central corneal thickness >600 µm in either eye - Advanced glaucoma - Significant ophthalmic disease - Modification of medication known to affect IOP		L: 18.6 T: 19.6 MD -1.0 (95% CI, -0.4 to -1.7); P = 0.002 **Week 6 – 12PM** L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -1.9); P<0.001 **Week 6 – 4PM** L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -2.0); P<0.001 **Month 3 – 8AM** L: 18.7 T: 19.7 MD -1.0 (95% CI, -0.4 to -1.7); P = 0.002 **Month 3 – 12PM** L: 17.9 T: 19.2 MD -1.3 (95% CI, -0.6 to -1.9); P<0.001 **Month 3 – 4PM** L: 17.8 T: 19.1 MD -1.3 (95% CI, -0.6 to -2.0); P<0.001 <u>Secondary Endpoints</u>: Proportion of patients with IOP ≤18 mmHg at all 9 time points: L: 22.9% T: 11.3% MD 11.6% (95% CI, 4.3-18.9); P=0.005 Proportion of patients with IOP reduction ≥25% from baseline at all time points: L: 34.9% T: 19.5% MD 15.3% (95% CI, 6.6-24.0); P=0.001	NA NA NA NA NA 12/9 15/7			**Applicability**: <u>Patient</u>: Patients had moderately increased IOP and the majority had been previously treated with a topical IOP-lowering therapy. The number of patients with an OAG diagnosis versus OH diagnosis was not provided. <u>Intervention</u>: Approved dose of latanoprostene treatment was used. <u>Comparator</u>: Timolol twice daily is an appropriate OAG treatment. <u>Outcomes</u>: IOP is an accepted surrogate outcome measure for patients with glaucoma. <u>Setting</u>: Forty-five sites in the United States and Europe.
2. Medeiros, et al[4] (Lunar) Phase 3, DB, MC, PG, NI, RCT	1. Latanoprostene Bunod 0.024% once daily at night (L) 2. Timolol 0.5% twice daily (T)	<u>Demographics</u>: Mean age: 65 years Female: 58% White: 71% Treatment naïve to topical IOP-lowering therapy: 28% Mean baseline IOP: 26.5 mmHg	<u>ITT</u>: 1. 278 2. 136 <u>PP</u>: 1. 259 2. 128	<u>Primary Endpoint</u>: Mean IOP (mmHg) at 8 AM, 12 AM and 4 PM at weeks 2, 6 and month 3 visits: **Week 2 – 8AM** L: 19.2 T: 19.6 MD -0.4 (95% CI, -1.1 to 0.3); P=0.216	NS	<u>Discontinuations due to adverse events:</u> L: 4 (1.4%) T: 1 (0.7%) P-value not reported	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (low) Randomized 2:1 by statistician prior to any study enrollment. Drug allocation was determined by Interactive Response Technology. <u>Performance Bias</u>: (low) See Apollo.

	3-month study	<u>Key Inclusion Criteria</u>: - OAG or OH in one or both eyes - 18 years of age or older - IOP ≥26 mmHg at a minimum of 1 of 3 time points, ≥24 mmHg at a minimum of 1 time point, ≥22 mmHg at 1 time point in the same eye and IOP ≤36 mmHg at all 3 measurement time points in both eyes at baseline - BCVA of +0.7 logarithm of the minimum angle of resolution or better in either eye. <u>Key Exclusion Criteria</u>: - Participation in any clinical trial within 30 days - Central corneal thickness >600 µm in either eye - Advanced glaucoma - Significant ophthalmic disease - Modification of medication known to affect IOP - Unable to discontinue contact lens use or other eye drop medications during and 15 min following study drug administration	<u>Attrition</u>: 1. 19 (7%) 2. 8 (6%)	**Week 2 – 12PM** L: 18.5 T: 19.2 MD -0.8 (95% CI, -1.4 to -0.1); P=0.022 **Week 2 – 4PM** L: 18.1 T: 18.8 MD -0.7 (95% CI, -1.3 to -0.1); P=0.025 **Week 6 – 8AM** L: 18.7 T: 19.6 MD -0.9 (95% CI, -1.6 to -0.3); P = 0.005 **Week 6 – 12PM** L: 18.0 T: 18.9 MD -0.8 (95% CI, -1.5 to -0.2); P=0.007 **Week 6 – 4PM** L: 17.9 T: 18.9 MD -1.0 (95% CI, -1.6 to -0.4); P=0.003 **Month 3 – 8AM** L: 18.7 T: 19.6 MD -0.9 (95% CI, -1.5 to -0.3); P = 0.006 **Month 3 – 12PM** L: 17.9 T: 19.2 MD -1.3 (95% CI, -1.9 to -0.7); P<0.001 **Month 3 – 4PM** L: 17.7 T: 19.1 MD -1.3 (95% CI, -2.0 to -0.7); P<0.001 <u>Secondary Endpoints</u>: Proportion of patients with IOP ≤18 mmHg at all 9 time points: L: 17.1% T: 11.1% MD 6.6% (95% CI, -0.4 to 13.5); P=0.84 Proportion of patients with IOP reduction ≥25% from baseline at all time points: L: 31.0%	NA NA NA NA NA NA NA NA 7/15	<u>Eye Irritation:</u> L: 20 (7.2%) T: 6 (4.4%) P-value not reported <u>Conjunctival Hyperemia:</u> L: 25 (9.0%) T: 1 (0.7%) P-value not reported		<u>Detection Bias</u>: (low) Patients and study site personnel were masked to treatment assignments. <u>Attrition Bias</u>: (high) Attrition was low (<10%); however, analysis was performed on the ITT (LOCF) population which is likely to show no difference between treatments in a noninferiority study and can bias the results. <u>Reporting Bias</u>: (low) See Apollo. **Applicability**: <u>Patient</u>: See above. Of the 72% of patients using IOP-lowering medication at enrollment, 81% were for prostaglandins followed by 24% for beta-blockers. <u>Intervention</u>: See Apollo. <u>Comparator</u>: See Apollo. <u>Outcomes</u>: See Apollo. <u>Setting</u>: Forty-six sites in the United States (40) and European Union (6).

				T: 18.5% MD 12.5% (95% CI, 4.0-21.1); P=0.007	13/8			

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; IOP = intraocular pressure; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NI = noninferiority; OH = ocular hypertension; OAG = open angle glaucoma; PG = parallel group; PP = per protocol

NEW DRUG EVALUATION: Netarsudil Dimesylate

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Netarsudil was studied in 2 published, double-blind, phase 3, multicenter, active treatment trials in patients with OAG or OH.[5] The studies, ROCKET-1 and ROCKET-2, employed the same methodology. Both studies were non-inferiority trials which reported results up to 3 months. The delta for non-inferiority was determined to be within 1.5 mmHg for all time points and 1.0 mmHg at a majority of time points (at least 5 of 9) for both trials.[11] The per-protocol population analysis was used for the primary analysis in both studies. Patients were included after screening, qualification 1 (medication washout if needed) and qualification 2 (stable IOP without medication) study visits. The primary endpoint was the decrease in IOP from baseline at 8AM, 10AM and 4PM at week 2, week 6 and month 3.

In the first study, ROCKET-1, netarsudil 0.02% once daily at night was compared to timolol 0.5% given twice daily (**Table 4**).[5] Patients (n=411) were predominately female (61%), mean age of 65 years, 66% had an open-angle diagnosis and the baseline IOP was 22.37 mmHg. Prior use of prostaglandins was found in 51% of patients. Patients were analyzed based on the per-protocol population with a maximum baseline IOP of 27 mmHg. Decreases from baseline in the netarsudil group ranged from 3.3-5.0 mmHg (15-22%) and 3.7 to 5.1 mmHg (17-22%) in the timolol group.[5] Netarsudil was not found to be non-inferior to timolol. In a post-hoc analysis, patients with an IOP of less than 25 were analyzed and netarsudil was found to be non-inferior to timolol. An analysis of the ITT population was not specifically reported but the authors mention that the results were similar to the per-protocol population.

The second study, ROCKET-2, compared netarsudil 0.02% daily and netarsudil 0.02% twice daily to timolol 0.5% twice daily (**Table 4**).[5] Patients enrolled in the trial were predominately white females with a mean age of 64 years. The mean baseline IOP for all groups was 21.46 mmHg. Sixty-six percent of patients had an OAG diagnosis and 34% were diagnosed with OH. Forty-eight percent of patients had previously used prostaglandins. Only patients with IOP less than 25 mmHg were included in the primary endpoint analysis. At month 3, the mean IOP decreases from baseline were 3.3 to 4.6 mmHg (16-21% reduction) in the netarsudil once daily group, 4.1 to 5.4 mmHg (22-24%) in the netarsudil twice daily group and 3.7 to 5.1 mmHg (18-23%) in the timolol group.[5] Netarsudil met the requirements for non-inferiority to timolol. An analysis of the ITT population was not specifically reported but the authors mention that the results were similar to the per-protocol population.

A third study was not published but was included in the FDA medical summary and will be briefly described.[11] The study was a phase 3, randomized, controlled trial in 708 adult patients with elevated IOP greater than 20 mmHg and less than 27 mmHg at the first qualification visit and greater than 17 mmHg and less than less than 27 mmHg at the second qualification visit. The study methodology was similar to the first two trials. Netarsudil 0.02% at night was compared to timolol 0.5% twice daily in both eyes. The primary endpoint was the decrease in IOP from baseline at 8AM, 10AM and 4PM at week 2, week 6 and month 3 analyzed in

the per-protocol population in patients with a maximum baseline IOP of less than 30 mmHg. Netarsudil was found to be non-inferior to timolol for the primary analysis of IOP of less than 30 mmHg in the per-protocol population but not in the ITT population.[11]

As discussed above, the use of a non-inferiority trial doesn't prove superior efficacy to existing products suggests that a new product is no worse than the comparator. The short-term duration of all the trials prevents conclusions on long-term use for netarsudil, in which chronic use is to be expected. Limited evidence would suggest that netarsudil is effective in patients with mild IOP elevations (less than 25 mmHg) and use in patients with more severe IOP is not known. The FDA summary found inconsistencies in supportive ITT analyses in netarsudil and timolol comparisons. Results that demonstrated non-inferiority in the per-protocol population were found to be inferior for ITT (LOCF) analyses in patients with higher baseline IOP values (27 mmHg or less in studies one and two and 30 mmHg or less in study 3). This reinforces the lack of robust data to support non-inferiority for netarsudil to timolol in populations with higher baseline IOP.

Clinical Safety:
The most common adverse reactions seen in trials of netarsudil were conjunctival hyperemia which occurred in 53% of patients treated with netarsudil compared to 8-10% of patients treated with timolol.[5] Other common adverse events seen in greater than 20% of patients treated with netarsudil were: corneal verticillata, instillation site pain, and conjunctival hemorrhage.[12] Conjunctival verticillata (deposits) are rarely seen with topical treatment but have been associated with systemic treatments such as amiodarone. They rarely cause visual disturbances and are usually reversible upon drug discontinuation. Discontinuations due to adverse events ranged from 10-30% in the netarsudil groups compared to 1-2% in timolol treated patients.

Table 3. Pharmacology and Pharmacokinetic Properties.[12]

Parameter	
Mechanism of Action	Netarsudil is a Rho kinase (ROCK) inhibitor. The exact mechanism is unknown but netarsudil is thought to work by reducing IOP via increased outflow of aqueous humor through the trabecular meshwork route.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not applicable
Elimination	Not applicable
Half-Life	Not provided
Metabolism	Metabolized via eye esterases

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual disturbance
2) Blindness
3) Intraocular pressure
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in intraocular pressure from baseline

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Serle, et al[5] (ROCKET-1) DB, RCT, NI, MC, PG	1. Netarsudil 0.02% ophthalmic solution once daily at night (N) 2. Timolol 0.5% ophthalmic solution twice daily (T) 3 months	Demographics: Mean Age: 65 years Female: 61% White: 75% Prior prostaglandin therapy: 51% OAG Diagnosis: 66% Mean baseline IOP: 22.37 mmHg Key Inclusion Criteria: - Open-angle glaucoma OR ocular hypertension in both eyes (OAG in one eye and OH in the fellow eye acceptable) - Age 18 years or older - Unmedicated IOP (after washout if required) >20 mmHg and <27 mmHg at 8 AM in at least one eye at both qualification visits and at the second qualification visit >17 mmHg and <27 mmHg at 10:00 AM and 4:00 PM (in the same eye) - If both eyes qualified then the eye with the higher IOP was selected as the study eye - If the IOP measurements were the same then the right eye was chosen as the study eye - Corrected visual acuity via ETDRS of +1.0 LogMAR or better in each eye Key Exclusion Criteria:	ITT: N: 202 T: 209 PP: N: 182 T: 188 Attrition: N: 20 (10%) T: 21 (10%)	Primary Endpoint: Mean IOP (mmHg) at 8 AM, 10 AM and 4 PM at weeks 2, 6 and month 3 visits in patients with baseline IOP <27 mmHg: **Week 2 – 8AM** N: 18.68 T: 18.33 MD 0.35 (95% CI, -0.27 to 0.96) **Week 2 – 10AM** N: 17.29 T: 17.55 MD -0.26 (95% CI, -0.87 to 0.36) **Week 2 – 4PM** N: 17.24 T: 17.70 MD -0.45 (95% CI, -1.08 to 0.17) **Week 6 – 8AM** N: 19.35 T: 18.24 MD 1.11 (95% CI, 0.42 to 1.80) **Week 6 – 10AM** N: 18.14 T: 17.44 MD 0.70 (95% CI, 0.04 to 1.36) **Week 6 – 4PM** N: 17.86 T: 17.71 MD 0.15 (95% CI, -0.52 to 0.83) **Month 3 – 8AM** N: 19.81 T: 18.47 MD 1.33 (95% CI, 0.64 to 2.03) **Month 3 – 10AM** N: 18.92 T: 17.96 MD 0.96 (95% CI, 0.26 to 1.66) **Month 3 – 4PM** N: 18.48 T: 17.74	NA for all due to methodology of NI trial	Ocular Adverse Events: N: 156 (77%) T: 92 (44%) p-value not reported Discontinuations due to Adverse Events: N: 20 (10%) T: 4 (2%) p-value not reported Conjunctival Hyperemia: N: 108 (53%) T: 17 (8%) P<0.0001 Conjunctival Hemorrhage: N: 27 (13%) T: 1 (0.5) P<0.0001 Conjunctival Verticillata: N: 11 (5%) T: 0 P=0.0004	NA NA 45/3 13/8 5/20	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized via a computer model. Performance Bias: (unclear) Vehicle bottle was provided for AM dosing of netarsudil once-daily treatment group. Masking of products was not described. Detection Bias: (low) Patients and study site personnel were blinded to treatment assignments. Attrition Bias: (low) Attrition was low in the both groups. Analysis was on the per-protocol population. Reporting Bias: (low) The study was funded by industry. Endpoints reported as originally designed. **Applicability**: Patient: Baseline IOP values would suggest mild IOP elevations. Results would be most applicable to white females with OAG. Post-hoc analysis of patients with an IOP <25 mmHg to showed more benefit than patients with higher IOP values. Intervention: Netarsudil dose is the FDA approved dose. Comparator: Timolol twice daily is an appropriate OAG treatment. Outcomes: IOP is an accepted surrogate outcome measure for patients with glaucoma. Setting: United States treatment centers.

		- Current use of >2 ocular hypertensive medicines - Pseudoexfoliation or pigment dispersion component glaucoma - Iridocorneal angle abnormalities or angle closure glaucoma - corneal thickness greater than 600 µm - Prior glaucoma surgery - Significant ocular disease - Pregnancy, nursing		MD 0.74 (95% CI, 0.07 to 1.42)				
2. Serle, et al[5] (ROCKET-2) DB, RCT, NI, MC, PG	1. Netarsudil 0.02% ophthalmic solution once daily at night (N) 2. Netarsudil 0.02% ophthalmic solution twice daily (N2) 3. Timolol 0.5% ophthalmic solution twice daily (T) 3 months (study duration up to 12 months and will be reported separately)	<u>Demographics</u>: Mean Age: 64 years Female: 61% White: 69% Prior prostaglandin therapy: 48% OAG: 66% Mean baseline IOP: 21.46 mmHg <u>Key Inclusion Criteria</u>: - Open-angle glaucoma OR ocular hypertension - Age 18 years or older OR children 0-2 years with OAG or OH (OAG in one eye and OH in the fellow eye acceptable) - Corrected visual acuity via ETDRS of +1.0 LogMAR or better in each eye - Unmedicated IOP (after washout, if required) >20 mmHg and <27 mmHg at 8 AM in at least one eye at both qualification visits and at the second qualification visit >17 mmHg and <27 mmHg	<u>ITT</u>: N: 251 N2: 253 T: 251 <u>PP</u>: N: 206 N2: 209 T: 217 <u>Attrition</u>: N: 45 (18%) N2: 44 (17%) T: 34 (14%)	<u>Primary Endpoint</u>: Mean IOP at 8 AM, 10 AM and 4 PM at weeks 2, 6 and month 3 visits in patients with baseline IOP <25 mmHg: **Week 2 – 8AM** N: 18.07 N2: 17.21 T: 17.69 *N vs. T:* MD 0.37 (95% CI, -0.25 to 0.99) *N2 vs. T: M*D -0.48 (-1.19 to 0.22) **Week 2 – 10AM** N: 16.72 N2: 16.35 T: 16.93 *N vs. T:* MD -0.21 (95% CI, -0.82 to 0.41) *N2 vs. T:* MD -0.57 (-1.24 to 0.09) **Week 2 – 4PM** N: 16.68 N2: 15.65 T: 16.83 *N vs. T:* MD -0.15 (95% CI, -0.75 to 0.46) *N2 vs. T:* MD -1.18 (-1.82 to -0.54) **Week 6 – 8AM** N: 17.95 N2: 17.64 T: 17.46 *N vs. T:* MD 0.49 (95% CI, -0.13 to 1.12) *N2 vs. T:* MD 0.17 (-0.51 to 0.86) **Week 6 – 10AM**	NA for all due to methodology of NI trial	<u>Ocular Adverse Events</u>: N: 182 (73%) N2: 213 (84%) T: 102 (41%) p-value not reported <u>Discontinuations due to adverse events</u>: N: 31 (12%) N2: 77 (30%) T: 2 (1%) p-value not reported <u>Conjunctival Hyperemia:</u> N: 126 (50%) N2: 149 (59%) T: 27 (11%) N vs. T: P<0.0001 N2 vs. T: P<0.0001 <u>Conjunctival Hemorrhage:</u> N: 37 (15%)	NA NA 39/3 48/2	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See ROCKET-1 <u>Performance Bias</u>: See ROCKET-1 <u>Detection Bias</u>: See ROCKET-1 <u>Attrition Bias</u>: (high) Attrition was high in all groups. Per-protocol analysis was used to analyze data. <u>Reporting Bias</u>: See ROCKET-1 **Applicability**: <u>Patient</u>: Baseline IOP values would suggest mild IOP elevations. Results would be most applicable to white females with OAG. <u>Intervention</u>: See ROCKET-1 <u>Comparator</u>: See ROCKET-1 <u>Outcomes</u>: See ROCKET-1 <u>Setting</u>: See ROCKET-1

		visit at 10:00 AM and 4:00 PM (in the same eye) - If both eyes qualified then the eye with the higher IOP was selected as the study eye - If the IOP measurements were the same then the right eye was chosen as the study eye <u>Key Exclusion Criteria</u>: - See Rocket-1		N: 16.95 N2: 16.28 T: 16.63 *N vs. T:* MD 0.32 (95% CI, -0.31 to 0.95) *N2 vs. T:* MD -0.34 (-1.02 to 0.2=33) **Week 6 – 4PM** N: 17.00 N2: 15.75 T: 16.60 *N vs. T:* MD 0.40 (95% CI, -0.22 to 1.02) *N2 vs. T:* MD -0.85 (-1.53 to -0.17) **Month 3 – 8AM** N: 18.24 N2: 17.58 T: 17.47 *N vs. T:* MD 0.77 (95% CI, 0.03 to 1.50) *N2 vs. T:* MD 0.11 (-0.64 to 0.86) **Month 3 – 10AM** N: 17.03 N2: 16.94 T: 16.92 *N vs. T:* MD 0.10 (95% CI, -0.59 to 0.80) *N2 vs. T:* MD 0.02 (-0.72 to 0.77) **Month 3 – 4PM** N: 17.13 N2: 16.51 T: 16.95 *N vs. T:* MD 0.18 (95% CI, -0.55 to 0.91) *N2 vs. T:* MD -0.44 (-1.16 to 0.27)		N2: 43 (17%) T: 0 (0) N vs. T: P<0.0001 N2 vs. T: P<0.0001 <u>Conjunctival Verticillata:</u> N: 22 (9%) N2: 37 (15%) T: 1 (0.4%) N vs. T: P<0.0001 N2 vs. T: P<0.0001	15/7 17/6 23%/5 15%/7	
<u>Abbreviations</u> [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; OAG = open-angle glaucoma; OH = ocular hypertension; PG = parallel group; PP = per protocol								

References:

1. National Institute for Health and Care Excellence. Glaucoma: diagnosis and management. NICE guideline 81. November 2017.

2. Canadian Agency for Drugs and Technologies in Health. Prostaglandin analogues for ophthalmic use: review of the comparative clinical effectiveness and cost-effectiveness. Rapid Response Report: Summary with Critical Appraisal. July 30, 2015.

3. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973. doi:10.1016/j.ophtha.2016.01.019

4. Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the lUNAR study. *Am J Ophthalmol*. 2016;168:250-259. doi:10.1016/j.ajo.2016.05.012

5. Serle JB, Katz LJ, McLaurin E, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: rho kinase elevated iop treatment trial 1 and 2 (rocket-1 and rocket-2). *Am J Ophthalmol*. 2018;186:116-127. doi:10.1016/j.ajo.2017.11.019

6. Jacobs D, Trobe, J, Sullivan, D. Open-angle glaucoma: epidemiology, clinical presentation, and diagnosis. *UpToDate*. January 2018.

7. Prum BE, Rosenberg LF, Gedde SJ, et al. Primary open-angle glaucoma preferred practice pattern(®) guidelines. *Ophthalmology*. 2016;123(1):P41-P111. doi:10.1016/j.ophtha.2015.10.053

8. Prum BE, Herndon LW, Moroi SE, et al. Primary angle closure preferred practice pattern(®) guidelines. *Ophthalmology*. 2016;123(1):P1-P40. doi:10.1016/j.ophtha.2015.10.049

9. Center For Drug Evaluation And Research. Application number: 207795Orig1s000. Clinical Review (s). Food and Drug Administration. October 31, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207795Orig1s000MedR.pdf. Accessed February 24, 2018.

10. Vyzulta Prescribing Information. Bausch + Lomb, a division of Valeant Pharmaceuticals. Bridgewater, NJ. 2017.

11. Center For Drug Evaluation And Research. Application Number: 208254Orig1s000; Clinical reviews. Food and Drug Administration. November 8, 2017. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208254Orig1s000MedR.pdf. Accessed: February 26, 2018.

12. Rhopressa® Prescribing Information. Aerie Pharmaceuticals, Inc., Irvine, CA. 2017.

Appendix 1: Current Preferred Drug List

Route	FormDesc	Brand	Generic	PDL
OP	DROPS	BETAXOLOL HCL	BETAXOLOL HCL	Y
OP	DROPS	ALPHAGAN P	BRIMONIDINE TARTRATE	Y
OP	DROPS	BRIMONIDINE TARTRATE	BRIMONIDINE TARTRATE	Y
OP	DROPS SUSP	AZOPT	BRINZOLAMIDE	Y
OP	DROPS	CARTEOLOL HCL	CARTEOLOL HCL	Y
OP	DROPS	COSOPT	DORZOLAMIDE HCL/TIMOLOL MALEAT	Y
OP	DROPS	DORZOLAMIDE-TIMOLOL	DORZOLAMIDE HCL/TIMOLOL MALEAT	Y
OP	DROPERETTE	COSOPT PF	DORZOLAMIDE/TIMOLOL/PF	Y
OP	DROPS	LATANOPROST	LATANOPROST	Y
OP	DROPS	XALATAN	LATANOPROST	Y
OP	DROPS	VYZULTA	LATANOPROSTENE BUNOD	Y
OP	DROPS	ISOPTO CARPINE	PILOCARPINE HCL	Y
OP	DROPS	PILOCARPINE HCL	PILOCARPINE HCL	Y
OP	GEL (GRAM)	PILOPINE HS	PILOCARPINE HCL	Y
OP	DROPS	TIMOLOL MALEATE	TIMOLOL MALEATE	Y
OP	DROPS	TIMOPTIC	TIMOLOL MALEATE	Y
OP	DROPS	TRAVATAN	TRAVOPROST	Y
OP	DROPS	TRAVATAN Z	TRAVOPROST	Y
IO	KIT	MIOCHOL-E	ACETYLCHOLINE CHLORIDE	N
OP	DROPS	APRACLONIDINE HCL	APRACLONIDINE HCL	N
OP	DROPERETTE	IOPIDINE	APRACLONIDINE HCL	N
OP	DROPS	IOPIDINE	APRACLONIDINE HCL	N
OP	DROPS SUSP	BETOPTIC S	BETAXOLOL HCL	N
OP	DROPS	BIMATOPROST	BIMATOPROST	N
OP	DROPS	LUMIGAN	BIMATOPROST	N
OP	DROPS	ALPHAGAN P	BRIMONIDINE TARTRATE	N
OP	DROPS	COMBIGAN	BRIMONIDINE TARTRATE/TIMOLOL	N
OP	DROPS SUSP	SIMBRINZA	BRINZOLAMIDE/BRIMONIDINE TART	N
IO	VIAL	MIOSTAT	CARBACHOL	N
OP	DROPS	DORZOLAMIDE HCL	DORZOLAMIDE HCL	N
OP	DROPS	TRUSOPT	DORZOLAMIDE HCL	N
OP	DROPS	PHOSPHOLINE IODIDE	ECHOTHIOPHATE IODIDE	N
OP	DROPS	BETAGAN	LEVOBUNOLOL HCL	N
OP	DROPS	LEVOBUNOLOL HCL	LEVOBUNOLOL HCL	N
OP	DROPERETTE	ZIOPTAN	TAFLUPROST/PF	N
OP	DROPS	BETIMOL	TIMOLOL	N
OP	DROP DAILY	ISTALOL	TIMOLOL MALEATE	N

OP	DROP DAILY	TIMOLOL MALEATE	TIMOLOL MALEATE	N
OP	SOL-GEL	TIMOLOL MALEATE	TIMOLOL MALEATE	N
OP	SOL-GEL	TIMOPTIC-XE	TIMOLOL MALEATE	N
OP	DROPERETTE	TIMOPTIC OCUDOSE	TIMOLOL MALEATE/PF	N
OP	DROPS	VYZULTA	LATANOPROSTENE BUNOD	N
OP	DROPS	RHOPRESSA	NETARSADIL DIMESYLATE	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to February Week 5 2018

Search Strategy:

#	Searches	Results
1	betaxolol.mp. or BETAXOLOL/	924
2	brimonidine.mp. or Brimonidine Tartrate/	1547
3	brinzolamide.mp.	258
4	carteolol.mp. or CARTEOLOL/	426
5	dorzolamide.mp.	885
6	latanoprost.mp.	1628
7	latanoprostene.mp.	9
8	pilocarpine.mp. or PILOCARPINE/	8380
9	TIMOLOL/ or timolol.mp.	4439
10	travoprost.mp. or TRAVOPROST/	546
11	acetylcholine.mp. or ACETYLCHOLINE/	87341
12	apraclonidine.mp.	430
13	bimatoprost.mp. or BIMATOPROST/	592
14	brimonidine.mp. or Brimonidine Tartrate/	1547
15	carbachol.mp. or CARBACHOL/	18323
16	echothiophate iodine.mp.	2
17	levobunolol.mp. or LEVOBUNOLOL/	292
18	tafluprost.mp.	139
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	116804
20	limit 19 to (english language and humans and yr="2014 -Current")	3868
21	limit 20 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or systematic reviews)	127

Appendix 3: Prescribing Information Highlights

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

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
One drop into the affected eye(s) once daily in the evening. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.2 mg/mL of netarsudil. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
The most common adverse reaction is conjunctival hyperemia (53%). Other common adverse reactions, approximately 20% include: corneal verticillata, instillation site pain, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aerie Pharmaceuticals, Inc. at 1-800-xxx-xxxx, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2017

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

VYZULTA (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use
Initial U.S. Approval: 2017

---------- INDICATIONS AND USAGE ----------
VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- DOSAGE AND ADMINISTRATION ----------
One drop in the affected eye(s) once daily in the evening. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Topical ophthalmic solution: 0.24 mg/mL latanoprostene bunod (0.024%) (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pigmentation: Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash changes: Gradual changes to eyelashes including increased length, increased thickness and number of eyelashes. Usually reversible upon discontinuation of treatment. (5.2)

---------- ADVERSE REACTIONS ----------
Most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2017