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Drug Class Update with New Drug Evaluation: Glaucoma Drugs

Date of Review: April 2023

Date of Last Review: May 2018
Dates of Literature Search: 03/01/2018 - 01/13/2023
Brand Name (Manufacturer): Omlonti (Santen Inc)
Dossier Received: yes

Generic Name: omidenepag isopropyl

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

Purpose for Class Update: The purpose of this class update is to evaluate the literature for new evidence to inform the medical management of glaucoma and to analyze the comparative effectiveness and harms of a newly approved topical therapy for glaucoma called omidenepag.

Plain Language Summary:

- The reason for this review is to look at the information used to evaluate medications for the treatment of glaucoma to see if any changes to need to be made to the current policy.
- A review done by the Agency for Health Research and Quality found that the different types of eye drops used for the treatment of glaucoma are better than no eye drops for reducing the pressure in the eye that cause glaucoma. The review also looked at two newer eye drops, called netarsudil and latanoprostene, and found they worked as well as the eye drops that have been available longer, such as latanoprost and timolol, but were also associated with more unwanted side effects of the eye.
- A review done by the Canadian Agency for Drugs and Technologies in Health reviewed a class of eye drops used for glaucoma called prostaglandins. They found that all the prostaglandin eye drops worked about the same, except for bitmatoprost, which worked a little better than the others. Side effects were similar for all of these types of eye drops.
- Another type of medication used for glaucoma is called netarsudil and it was recently reviewed by the Cochrane Database for Systematic Reviews and found that this type of eye drop was better than saline drops at reducing pressure in the eye. It was not found to be better than two other drugs that are commonly used for glaucoma, called timolol and latanoprost.
- An organization that provides guidelines, called the National Institute for the Health and Care Excellence, updated their recommendations for the treatment of glaucoma support our current policy.
- A preservative-free eyedrop formulation of latanoprost (XELPROS) was recently approved by the Food and Drug Administration. A combination product containing latanoprost and netarsudil (ROCKLATAN) was also approved. Both medicines are used to reduce eye pressure in people with glaucoma.
- One new safety warning was issued by the Food and Drug Administration for betaxolol because it may reduce how fast the heart beats and lower blood pressure.

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- A newly approved eye drop by the Food and Drug Administration is called omidenepag. It was studied in people with glaucoma and high pressures in the eye, which found that it worked about as well as latanoprost and timolol, other drugs used for the same conditions.
- Based on this review, the Drug Use Research Management group recommends no changes to the current policy for the treatment of glaucoma.

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 omidenepag would be safer or more effective than other available ophthalmic treatments for glaucoma?

Conclusions:

- New evidence for this review was available from 3 new systematic reviews and meta-analyses, one new guideline, 2 new formulations, one new safety alert and one new drug approval.
- A high quality systematic review and meta-analysis by Agency for Health Research and Quality (AHRQ) found that topical medications (e.g., beta-blockers, prostaglandins, alpha agonists and carbonic anhydrase inhibitors) were superior to placebo, or no treatment, in reducing IOP (mean difference [MD] -3.14 mm Hg; 95% confidence interval [CI], -4.19 to -2.08, I^2 = 95%) based on moderate quality of evidence.[1] Newer topical therapies, netarsudil and latanoprostene, were found to reduce IOP to a similar extent or slightly more than traditional topical agents for open-angle glaucoma (OAG) and ocular hypertension (OHT).[1] Netarsudil and latanoprostene were associated with more ocular adverse events compared to other topical medications.
- A Canadian Agency for Drugs and Technologies in Health (CADTH) review of ophthalmic prostaglandin analogues found no major differences in IOP lowering between the therapies; however, bitmatoprost was consistently shown to produce the most IOP lowering of all the therapies (moderate quality of evidence).[2] Adverse events (e.g., conjunctival hyperemia, keratitis, and follicular conjunctivitis) were found to be similar among the prostaglandins.
- A Cochrane review found that there was low quality evidence that netarsudil was more effective at lowering IOP than placebo (MD 3.11 mm Hg; 95% CI, 2.59 to 3.62). Timolol and latanoprost were found to be more effective at lowering IOP, MD 0.66 mm Hg and 0.97 mm Hg, respectively (low and moderate quality of evidence).[3]
- Updated guidance on the management of glaucoma by the National Institute for the Health and Care Excellence (NICE) supports the current Oregon Health Plan (OHP) policy for glaucoma therapies.[4]
- A preservative free version of latanoprost (XELPROS) and a combination product containing latanoprost and netarsudil (ROCKLATAN) were approved to reduce IOP in people with OAG and OHT.[5,6]
- One new safety alert was identified for betaxolol warning of minor decreases in heart rate and reduced blood pressure.[7]
- Omidenepag is a new prostaglandin analog used to lower IOP in people with OAG or OHT. Participants in the studies had a baseline IOP of 24-26 mmHg with low quality evidence demonstrating reductions at 3 months of 5.4 to 7.4 mmHg, which was noninferior to latanoprost once daily or timolol twice daily.[8] Common adverse events associated with the use of omidenepag are conjunctival hyperemia, photophobia, vision blurred, dry eye, instillation site pain, eye pain, ocular hyperemia, punctate keratitis, headache, eye irritation and visual impairment.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the current evidence.
- Maintain omidenepag as non-preferred on the PDL.

- After evaluation of costs in executive session, brimonidine tartrate 0.1% ophthalmic drops were designated as preferred.

Summary of Prior Reviews and Current Policy

- The OHP provides coverage for glaucoma with the current policy preferring treatments from each class of therapies; miotics, alpha- adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues.
- The is no evidence of 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 1,700 Oregon Health Plan (OHP) fee-for-service (FFS) patients with a diagnosis of glaucoma with treatments having a minimal impact on overall OHP healthcare costs.

Background:

Glaucoma is a collection of eye diseases resulting from optic nerve damage that can lead to vision loss and blindness. Glaucoma is the second leading cause of blindness in the world.[9] Glaucoma is characterized by two variations: OAG and closed or narrow-angle 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.[10] The suggested incidence of narrow-angle glaucoma is 20 million people worldwide.[11] Open-angle glaucoma is more common in individuals of European and African decent and the incidence of narrow angle 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.[9] Risk factors for patients with angle-closure glaucoma are family history, age over 60 years, female, hyperopia (farsightedness), certain medications, race and pseudoexfoliation (age related systemic syndrome that effect the eye).

Open-angle glaucoma is a more chronic condition while narrow-angle glaucoma often occurs suddenly and is considered a medical emergency. Both types are a result of inadequate drainage of the eye causing IOP. 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.[12] 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.[9] Narrow-angle 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. Narrow-angle glaucoma is caused by certain anatomical traits of the eye. Acute blockage of the entire angle in narrow-closure glaucoma can cause rapidly rising IOP and subsequent vision loss and potential blindness if not treated. Chronic narrow-angle glaucoma can occur over time and result in scarring of the optic nerve.[9] 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 two IOP readings of more than 22 mmHg, with normal ranges of IOP being 8-21 mm Hg.[9] Treatment options for lowering IOP include medications, laser therapy 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),

alpha adrenergic agonists (e.g., brimonidine, apraclonidine), Rho kinase inhibitors (RKi) (e.g., netarsudil) and nitric oxide-donating therapy (e.g., latanoprostene bunod).[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 them from being an initial treatment option. Topical carbonic anhydrase inhibitors have been shown to be less effective than other options and are associated with burning, stinging and allergic reactions.[12] 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.[12]

Acute treatment of angle-closure glaucoma includes methods to lower quickly reduce IOP.[9] 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.[10] 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, and presence of disc hemorrhages.[10] There is no standard IOP target; however, IOP lowering of 25-30% (approximately 6-7 mmHg) below IOP at presentation has been suggested.[9,11,13] Evidence has shown that lowering IOP slows progression of visual impairment, and potential blindness associated with elevated IOP levels.

The overall cost per quarter for glaucoma medications in the fee-for-service (FFS) population is not significant. There is about 95% preferred drug utilization for the class. As expected, the highest utilization is within the prostaglandin class followed by alpha 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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

AHRQ – Screening for Glaucoma in Adults: A Systematic Review for the U.S. Preventative Task Force

In 2022 AHRQ evaluated the evidence for the management and treatment of glaucoma with literature updated through January 21, 2022.[1] There were 83 studies included in the review (n=75,887).[1] The mean age ranged from 61 to 66 years and females accounting for 50% to 68% of the participants. For the purpose of this update, the focus will be on new evidence related to the treatment of glaucoma. There were two key questions related to drug therapy: the effects of newer agents (e.g., netarsudil and latanoprostene bunod) compared to older therapies and the harms of newer therapies compared to older products.

There was moderate quality evidence from 16 trials (n=3,706) that topical medication (e.g., beta-blockers, prostaglandins, alpha agonists and carbonic anhydrase inhibitors) were superior to placebo, or no treatment, in reducing IOP (MD -3.14 mm Hg; 95% CI, -4.19 to -2.08, I^2 = 95%) (Table 1).[1] High heterogeneity reduces the confidence in these findings; however, the estimate of effect is precise. Topical medical treatment was associated with decreased risk of progression of vision loss compared to placebo (relative risk [RR] 0.68; 95% CI, 0.49 to 0.96; I^2 = 53%; moderate strength of evidence). Serious adverse events or withdrawals due to adverse events were similar between treatment and placebo (low quality of evidence).[1] Ocular adverse events (e.g., redness, burning, irritation, itching, tearing) were increased with topical medication compared to placebo based on two trials (RR 1.21; 95% CI, 1.10 to 1.33 and RR 3.52; 95% CI, 2.46 to 5.02; low quality of evidence).[1]

Table 1. Topical Medications compared to Placebo/No Treatment (pooled analyses)[1]

Drug Class	Number of Trials	N	Estimates (95% CI)	I^2
Beta-blockers	9	455	MD -3.75 (-5.43 to -2.06)	92%
Prostaglandins	1	516	MD -2.70 (-3.34 to -2.06)	NA
Alpha agonists	1	30	MD -2.30 (-3.52 to -1.08)	NA
Carbonic anhydrase inhibitors	4	1,635	MD -1.20 (-2.30 to -0.61)	0%
Mixed/various medications	1	817	MD -4.60 (-4.85 to -4.35)	NA
Abbreviations: MD = mean difference; NA = not applicable				

Moderate evidence demonstrated newer topical therapies, netarsudil and latanoprostene, reduced IOP by a similar margin or greater efficacy than older medications. Three fair quality trials, in participants with OAG and OHT, evaluated the effectiveness of netarsudil compared to timolol for the outcome of IOP lowering at 3 and 12 months.[1] Netarsudil was found to be noninferior to timolol. Comparative evidence from a pooled analysis of two trials found similar IOP lowering for netarsudil and latanoprost at 12 months. The likelihood of patients achieving an IOP of 18 mm Hg or less at 12 months was similar for netarsudil and latanoprost, 57.4% and 65.5%, respectively (RR 0.73; 95% CI, 0.61 to 0.88; $p<0.05$).[1] A trial evaluating latanoprostene found more IOP lowering, by a small amount (1.2 mm Hg) compared to latanoprost at 1 month. Latanoprostene bunod demonstrated greater reductions of IOP compared to timolol by a mean difference of -1.0 to -1.3 mm Hg (2 trials). An additional pooled analysis of latanoprostene compared to timolol found latanoprostene to have an increased likelihood of IOP equal to or less than 18 mm Hg, 20.2% and 11.2% (p=0.001) at 3 months.[1] When compared to timolol, netarsudil was associated with an increased risk of adverse ocular events and withdrawals due to adverse events, based on moderate evidence. Latanoprostene was associated with an increased risk of ocular events compared to timolol (RR 1.72; 95% CI, 1.22 to 2.42; moderate quality evidence) based on data from two pooled trials (n=840) .[1] Latanoprostene and latanoprost were associated with a similar risk of adverse events and withdrawals due to adverse events.

CADTH – Prostaglandin Analogues for Ophthalmic Use

The evidence for the use of prostaglandin analogues in adults to reduce IOP was the focus of a CADTH report. Bimatoprost monotherapy or in combination with timolol was compared to latanoprost (monotherapy or in combination with timolol), latanoprostene, travoprost (monotherapy or in combination with timolol) or tafluprost.[2] Thirteen publications met the inclusion criteria; 5 systematic reviews, 7 randomized controlled trials, and one cost-effectiveness analysis. Participants in the trials were adults (18 years or older and mean age of 31 to 64 years) diagnosed with glaucoma or glaucomatous conditions (e.g., primary open-angle glaucoma [POAG], OAG, OHT, normal tension glaucoma [NTG] and pseudo-exfoliative glaucoma [PXG]). Participants were both treatment naïve and treatment experienced. Trials were conducted in the United States (U.S,), China, Australia, Canada, and Japan.[2] Conflicts of interest were noted in one of the systematic reviews. Risk of bias for the systematic reviews was mixed, based on the authors' assessment. The included RCTs were found to be well representative of patients with glaucoma and while there were some issues with blinding and randomization, the overall study quality was fair. The primary outcome in all systematic reviews was change in IOP.

Bimatoprost, travoprost, latanoprost, and tafluprost were all associated with a 15% to 20% reduction in IOP, with no major delineation in clinical differences.[2] Three to six month pooled analysis data on the use of bimatoprost demonstrated more reduction in IOP compared to latanoprost and travoprost; with bitmatoprost having the greatest IOP lowering effect and latanoprost have the weakest effect.[2] The clinical effectiveness of the prostaglandin analogues on ocular pressure was determined to be similar by the authors. Ocular perfusion pressure, as an indirect measurement of vascular profusion of the posterior ocular segment that is linked to IOP, was measured and lowering was compared between the prostaglandin analogues. There were no statistically significant differences found between the bimatoprost and latanoprost/timolol for ocular perfusion pressure.

Adverse events were found to be similar between the prostaglandin analogues. The most common adverse events were conjunctival hyperemia, keratitis, and follicular conjunctivitis. One meta-analysis found that conjunctival hyperemia was more common with bimatoprost and travoprost when compared to latanoprost.[2]

Cochrane – Rho kinase Inhibitor for Primary Open-angle Glaucoma and Ocular Hypertension

Cochrane performed a systematic review and meta-analysis in 2022 to evaluate the comparative effectiveness and safety profile of RKi compared to placebo and other active treatments. Seventeen trials lasting up to 12 months met inclusion criteria.[3] Trials included adult participants (n=4953) with a diagnosis of OAG, POAG or OHT.[3] Rho kinase inhibitors, netarsudil and ripasudil (not available in the US), were studied as monotherapies or in combination with latanoprost or timolol and compared to placebo, latanoprost, timolol or netarsudil. The risk of bias was found to be low in seven trials, moderate in three trials and high in three.

Data from 3 RCTs (n=155) of netarsudil compared to placebo, netarsudil was found to lower IOP more than placebo (MD 3.11 mm Hg; 95% CI, 2.59 to 3.62; low quality evidence).[3] Low quality evidence from three trials (n=1415) found timolol to be superior to netarsudil by a MD of -0.66 mmHg (95% CI, 0.41 to 0.91). Latanoprost was also found to lower IOP more than netarsudil (MD 0.97 mm Hg; 95% CI, 0.67 to 1.27; moderate quality evidence).[3] Combination therapy of netarsudil and latanoprost was more effective than latanoprost monotherapy at lowering IOP, measured at 6 months, by a MD of 1.64 mm Hg (95% CI, 1.11 to 2.16) based on moderate quality evidence; however, there were more adverse events in the combination therapy group, 26 more per 100 person-months (low quality evidence).[3] There was moderate quality evidence that the combination of netarsudil in combination with latanoprost was more effective than netarsudil monotherapy (MD 2.66 mm Hg; 95% CI, 2.35 to 2.98) with a similar risk of adverse events. The combination of netarsudil and timolol was slightly more effective than timolol alone, a MD of 0.75 mm Hg (95% CI, 0.21 to 1.29) with more adverse reactions in the combination group, 35 more events per 100 person-months (moderate quality evidence for both).[3] Overall, RKi were not associated with any serious adverse events.

After review, thirteen systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14–17,18–25]

New Guidelines:

High Quality Guidelines:

NICE – Glaucoma: Diagnosis and Management

In 2022 NICE updated their 2017 recommendations for the treatment of glaucoma.[4] Treatment should be considered for people with OHT and an IOP of 24 mm Hg, if the patient is at risk of visual impairment in their lifetime and not a candidate for selective laser trabeculoplasty (SLT). Initial pharmacotherapy recommendations include the use of a generic prostaglandin analogue for people with OHT or chronic open-angle glaucoma (COAG). For those people who are unable to tolerate a prostaglandin analogue, another generic prostaglandin analogue should be considered. Beta-blockers are recommended as second line therapy. Other options include a non-generic prostaglandin, carbonic anhydrase inhibitor, sympathomimetic, miotic or a combination of therapies.[4] People with an IOP of 24 mm Hg or higher despite current therapy should be offered a medication from an alternate therapeutic class (e.g., beta-blocker, carbonic anhydrase inhibitor or sympathomimetic). Combination therapy of medications from different therapeutic classes may be needed to adequately reduce IOP. Preservative free eye drops should be reserved for people who have an allergy to preservatives or ocular surface disease which is considered clinically significant and are at high risk of conversion to COAG. Treatment is not recommended for those people with suspected COAG but have an IOP less than 24 mm Hg unless they are at risk of visual impairment.[4] Pharmacotherapy may be discontinued in people with OHT or suspected COAG if they have a low risk of becoming visually impaired and an acceptable IOP. If therapy is discontinued, reassessment of IOP should be done within one to four months. People who have had surgery and have COAG whose IOP has not been reduced to a level to prevent sight loss may consider pharmacological treatment, and potentially combination therapy from two different classes.[4]

After review, two guidelines were excluded due to poor quality or not applicable to the review.[13,26]

New Formulations or Indications:

New Formulations:

XELPROS (latanoprost ophthalmic emulsion 0.005%) – A new formulation of latanoprost ophthalmic emulsion was approved in September of 2018.[6] XELPROS is a prostaglandin F2alpha analog used to reduce IOP in people with OAG or OHT. It differs from other latanoprost products because it is not formulated with benzalkonium chloride (BAK), a commonly used preservative. Studies in participants with a baseline IOP of 23-26 mmHg demonstrated mean reductions of 6-8 mm Hg.[6] XELPROS is given once daily in the evening in the affected eye at 12 weeks.

ROCKLATAN (netarsudil/latanoprost) – A combination product containing a RKi and a prostaglandin F2α analogue (netarsudil 0.02% and latanoprost 0.005%) was approved in March 2019 for the use in people with IOP or OHT to reduce elevated IOPs.[5] ROCKLATAN was approved based on two randomized controlled trials (RCTs) which found the combination product to lower IOP 1-3 mm Hg more than the monotherapy components over 3 months.[5]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Betaxolol[7]	Betoptic S®	June 2021	Warning	Betaxolol has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S should be discontinued at the first signs of cardiac failure.

Randomized Controlled Trials:
A total of 140 citations were manually reviewed from the initial literature search. After further review all 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).

NEW DRUG EVALUATION:
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Omidenepag is a prostaglandin analog approved in September of 2022 for the reduction of elevated IOP in patients with OAG or OHT.[27] Omidenepag works by being a relatively selective prostaglandin E2 (EP2) receptor agonist and is thought to increase uveoscleral outflow of aqueous humor. Omidenepag 0.002% solution is administered in the affected eye once a day at night.[27]

Omidenepag was approved based on 3, nonpublished, RCTs.[8] Due to the unavailability of published data, the evidence cannot be critically evaluated. Data in **Table 4** is based on the FDA Clinical Review.[8] All trials included participants with open-angle glaucoma or ocular hypertension with a baseline IOP of 24-26 mmHg.[8] Studies lasted 3 months. The primary endpoint was the non-inferiority (NI) of omidenepag compared to active treatment at month 3. For all studies, the non-inferiority was determined by the upper limit of the 2-sided 95% CI for the difference in the mean IOP of equal to or less than 1.5 mmHg at all 9 timepoints and equal to and less than 1.0 mmHg at a majority (5 or more) of the 9 timepoints. Secondary endpoints were considered exploratory.

The FDA concluded that compared to latanoprost 0.005% and timolol maleate 0.5% solution, changes in mean IOPs were not clinically significantly different with omidenepag; however, reductions in IOP obtained with omidenepag were considered clinically meaningful.[8] Reduction in mean IOPs from baseline were -6.0 mmHg for those treated with omidenepag compared to a reduction of -6.1 mmHg with timolol in one study (NI achieved) and -6.2 in the second study (NI not achieved). Omidenepag decreased mean IOPs by 6.5 mm Hg when compared to latanoprost which decreased IOPs by 7.0 mmHg (NI achieved).

Additional evidence includes four published trials. Three trials were excluded due to quality and study design; one was a dose -ranging phase 2 study (SPECTRUM-6), the second study was a small (n=26), single arm, open-label study in exclusively Japanese patients (FUJI) and the third study was an open-label, phase 3 study (RENGE) evaluating the durability of IOP reductions at 52 weeks but lacked statistical comparison between the groups.[28–30]

In a poor quality, phase 3 trial omidenepag was compared to latanoprost in a NI study enrolling 190 participants. Participants were included if they had a baseline IOP of 22 mm Hg or higher in at least one eye and 34 mm Hg or less in both eyes at 3 timepoints.[31] If both eyes met the criteria, then the eye with the higher mean diurnal IOP at baseline was used, if they were the same then the right eye was designated the study eye. The primary endpoint was the change in mean diurnal IOP from baseline to week 4. Noninferiority was determined if they upper limit of thee 95% CI was at or below the NI margin of 1.5 mm Hg. Reductions in IOP were similar between groups at 4 weeks. Omidenepag decreased mean IOP by -5.93 mm Hg and latanoprost reduced IOP by -6.56 mm Hg (MD 0.63 mm Hg; 95% CI, 0.01 to 1.26; P=0.048).[31] Omidenepag was found to be noninferior to latanoprost, with significantly less IOP lowering but the difference is unlikely to be clinically meaningful. Limitations to these findings include short trial duration, randomization and medication preparation that could lead to study drug unmasking, and lack of methodological details on study procedure.

Clinical Safety:

The most common adverse effects associated with the use of omidenepag in 1% or greater of the people treated are: conjunctival hyperemia, photophobia, vision blurred, dry eye, instillation site pain, eye pain, ocular hyperemia, punctate keratitis, headache, eye irritation and visual impairment.[27] There are warnings for the risk of pigmentation of the iris, which is often permanent, due to an increase in melanin content in the melanocytes. Pigmentation in the periorbital tissue and eyelashes are most likely reversible.[27] Eyelashes and vellus hair may be increased in length, thickness and in number which are most likely reversible upon discontinuation. Ocular inflammation and macular edema have also occurred with omidenepag use. There are no contraindications for the use of omidenepag.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) IOP reduction
2) Duration of IOP reduction
3) Visual field changes
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) IOP reduction at 3 months

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Omidenepag is a relatively selective E2 (EP2) receptor agonist which decreases IOP due to ocular hypotensive activity
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not applicable
Elimination	83% feces and 4% urine
Half-Life	Not described
Metabolism	Omidenepag isopropyl is rapidly metabolized in the eye to omidenepag by carboxylesterase-1 and further metabolized in the liver through oxidation, N-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation.

Abbreviations: IOP = intraocular pressure

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. Study 01171505[8] Phase 3 MC, NI, RCT, SB	1. Omidenepag 0.002% solution once daily in the evening in the affected eye 2. Latanoprost 0.005% solution once daily in affected eye Study duration: 3 months	Demographics: Age: 54.6 years Male: 52.6% Asian: 100% Key Inclusion Criteria: - OAG or OHT Key Exclusion Criteria: - Not described	ITT: 1. 184 2. 185 PP: 1. 170 2. 177 Attrition: 1. 15 (8.1%) 2. 8 (4.3%)	Primary Endpoint: Diurnal IOP reduction IOP in the study eye at month 3 (Upper CI)*: 1. -6.5 mm Hg 2. -7.0 mm Hg LSMD 0.5 mm Hg (95% CI, -0.2 to 1.1) NI was achieved Secondary Endpoints: All secondary endpoints were considered exploratory	NA for all	Discontinuations due to adverse events: 1. 4 (2.2%) 2. 2 (1.1%) Conjuntiva hyperemia: 1. 18 (9.7%) 2. 7 (3.8%) Photophobia: 1. 6 (3.2%) 2. 1 (0.5%) Ocular hyperemia: 1. 3 (1.6%) 2. 2 (1.1%)	NA for all	**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results are most applicable to patients in their mid-fifties who are Asian. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: Latanoprost is an appropriate comparator. Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: India, Taiwan, Korea and Singapore
2. Study 011091N† SPECTRUM 3 Phase 3 DB, MC, RCT	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Timolol 0.5% twice daily in affected eye Study duration: 3 months	Demographics: Age: 64.1 years Male: 39.3% Asian: 0.9% White: 74.2% Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 212 2. 213 PP: 1. 189 2. 204 Attrition: 1. 22 (10.4%) 2. 11 (5.1%)	Primary Endpoint: IOP in the study eye at month 3 (Upper CI)*: 1. -6.0 mm Hg 2. -6.2 mm Hg LSMD 0.8 mm Hg (95% CI, 0.2 to 1.4) Did not meet NI criteria Secondary Endpoints: See above		Discontinuations due to adverse events: 1. 10 (4.7%) 2. 3 (1.4%) Conjuntiva hyperemia: 1. 10 (4.7%) 2. 7 (3.3%) Photophobia: 1. 9 (4.3%) 2. 1 (0.5%) Ocular hyperemia: 1. 5 (2.4%) 2. 3 (1.4%)		**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results are most applicable to people who are in their 60s and are White who have OAG or OHT. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: see above Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: See above

3. Study 0117101N†[8] SPECTRUM 4 DB, MC, RCT Phase 3	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Timolol 0.5% twice daily in affected eye Study duration: 3 months	Demographics: Age: 64 years Male: 89.5% Asian: 3.9% White: 64% Key Inclusion Criteria: - OAG, OHT and pediatric glaucoma Key Exclusion Criteria: - Not described	ITT: 1. 204 2. 205 PP: 1. 187 2. 196 Attrition: 1. 17 (8.3%) 2.9 (4.4%)	Primary Endpoint: IOP in the study eye at month 3 (Upper CI)*: 1. -6.0 mm Hg 2. -6.1 mm Hg LSMD 0.1 mm Hg (95% CI, 0.7 to -0.5) NI was achieved Secondary Endpoints: See above		Discontinuations due to adverse events: 1. 13 (6.4%) 2. 3 (1.5%) Photophobia: 1. 8 (3.9%) 2. 0 (0%) Ocular hyperemia: 1. 3 (1.5%) 2. 2 (1.0%)		**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results pertain mostly to White males in their 60s. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: Timolol is an appropriate comparator. Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: United States
4. Aihara[31] AYAME MC, NI, PG, RCT Phase 3	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Latanoprost 0.005% once daily in affected eye Study duration: 4 weeks	Demographics: Age: 63.6 years Male: 45% Asian: 100% Baseline IOP: 23.59 mmHg Prior use of IOP medications: 51.3% Key Inclusion Criteria: - Bilateral POAG or OHT - 20 years or older - Baseline IOP of 22 mm Hg or higher in at least one eye and 34 mm Hg or less in both eyes at 3 timepoints Key Exclusion Criteria: - Visual field depression that was severe or at risk of progression during the study - Corneal abnormality or other condition potentially interfering with reliable Goldmann applanation tonometry - presence of any active external ocular disease, inflammation or infection of the eye or eyelids - history of other eye diseases - history of eye surgery - Pregnant people	ITT: 1. 94 2. 96 PP: 1. 92 2. 95 Attrition: 1. 2 (2.1%) 2. 1 (1%)	Primary Endpoint: Change from baseline in mean diurnal IOP at week 4: 1. -5.93 mm Hg 2. -6.56 mm Hg MD 0.63 mm Hg (95% CI, 0.01 to 1.26) P=0.048 NI was met (the NI margin was 1.5 mmHg) Per Protocol Population: Change from baseline in mean diurnal IOP at week 4: MD 0.65 mm Hg (95% CI, 0.02 to 1.28) P=0.048		Discontinuations due to adverse events: 1. 2 (2.1%) 2. 2 (2.1%) Conjunctiva hyperemia: 1. 23 (24.5%) 2. 10 (10.4%) Photophobia: 1. 4 (4.3%) 2. 0 Overall drug adverse reactions: 1. 37 (39.4%) 2. 18 (18.8%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (high) Randomized 1:1 by the permuted block method by the study medication randomization manager who prepared study medication and medication codes. Performance Bias: (unclear) Investigators and observers were blinded but details not provided. Boxes for medications were the dame but eyedrop bottles were different. Detection Bias: (unclear) Not described. Attrition Bias: (low) Attrition was low in both groups. Handling of missing data was not described. Reporting Bias: (low) Study conducted per protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to participants who are Asian and slightly older than the average person with POAG. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: see above Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: Japan
Key: * Noninferiority margin determined by the upper limit of the 2-sided 95% CI for the difference in the mean IOP of equal to or less than 1.5 mmHg at all 9 timepoints and equal to and less than 1.0 mmHg at a majority (5 or more) of the 9 timepoints; † Studies were identical in design and methods; however, study 01109IN had a 9-month open label treatment period.								

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; DB = double blind; IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OAG = open angle glaucoma; OHT = ocular hypertension; PP = per protocol; POAG = primary open-angle glaucoma; RCT = randomized controlled trial; SB = single blind

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
betaxolol HCl	BETAXOLOL HCL	DROPS	Y
brimonidine tartrate	ALPHAGAN P	DROPS	Y
brimonidine tartrate	BRIMONIDINE TARTRATE	DROPS	Y
brinzolamide	AZOPT	DROPS SUSP	Y
brinzolamide	BRINZOLAMIDE	DROPS SUSP	Y
carteolol HCl	CARTEOLOL HCL	DROPS	Y
dorzolamide HCl/timolol maleat	COSOPT	DROPS	Y
dorzolamide HCl/timolol maleat	DORZOLAMIDE-TIMOLOL	DROPS	Y
dorzolamide/timolol/PF	COSOPT PF	DROPERETTE	Y
dorzolamide/timolol/PF	DORZOLAMIDE-TIMOLOL	DROPERETTE	Y
latanoprost	LATANOPROST	DROPS	Y
latanoprost	XALATAN	DROPS	Y
latanoprost	XELPROS	DRPS EMULS	Y
pilocarpine HCl	ISOPTO CARPINE	DROPS	Y
pilocarpine HCl	PILOCARPINE HCL	DROPS	Y
timolol maleate	TIMOLOL MALEATE	DROPS	Y
timolol maleate	TIMOPTIC	DROPS	Y
travoprost	TRAVATAN Z	DROPS	Y
travoprost	TRAVOPROST	DROPS	Y
acetylcholine chloride	MIOCHOL-E	KIT	N
apraclonidine HCl	IOPIDINE	DROPERETTE	N
apraclonidine HCl	APRACLONIDINE HCL	DROPS	N
betaxolol HCl	BETOPTIC S	DROPS SUSP	N
bimatoprost	BIMATOPROST	DROPS	N
bimatoprost	LUMIGAN	DROPS	N
brimonidine tartrate	ALPHAGAN P	DROPS	N
brimonidine tartrate/timolol	BRIMONIDINE TARTRATE-TIMOLOL	DROPS	N
brimonidine tartrate/timolol	COMBIGAN	DROPS	N
brinzolamide/brimonidine tart	SIMBRINZA	DROPS SUSP	N
carbachol	MIOSTAT	VIAL	N
dorzolamide HCl	DORZOLAMIDE HCL	DROPS	N
dorzolamide HCl	TRUSOPT	DROPS	N
echothiophate iodide	PHOSPHOLINE IODIDE	DROPS	N
latanoprostene bunod	VYZULTA	DROPS	N
levobunolol HCl	LEVOBUNOLOL HCL	DROPS	N
netarsudil mesylat/latanoprost	ROCKLATAN	DROPS	N
netarsudil mesylate	RHOPRESSA	DROPS	N

pilocarpine HCl	VUITY	DROPS	N
tafluprost/PF	TAFLUPROST	DROPERETTE	N
tafluprost/PF	ZIOPTAN	DROPERETTE	N
timolol	BETIMOL	DROPS	N
timolol maleate	ISTALOL	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	SOL-GEL	N
timolol maleate	TIMOPTIC-XE	SOL-GEL	N
timolol maleate/PF	TIMOLOL MALEATE	DROPERETTE	N
timolol maleate/PF	TIMOPTIC OCUDOSE	DROPERETTE	N
bimatoprost	DURYSTA	IMPLANT	
tafluprost/PF	TAFLUPROST	DROPERETTE	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 13, 2023

Search Strategy:

#	Searches	Results
1	betaxolol.mp. or Betaxolol/	1022
2	brimonidine.mp. or Brimonidine Tartrate/	1967
3	brinzolamide.mp.	434
4	carteolol.mp. or Carteolol/	484
5	dorzolamide.mp.	1176
6	latanoprost.mp. or Latanoprost/	2168
7	pilocarpine.mp. or Pilocarpine/	9869
8	Timolol/ or timolol.mp.	5359
9	travoprost.mp. or Travoprost/	755
10	acetylcholine.mp. or Acetylcholine/	100439
11	apraclonidine.mp.	479
12	bimatoprost.mp. or Bimatoprost/	903
13	brimonidine.mp. or Brimonidine Tartrate/	1967
14	carbachol.mp. or Carbachol/	19263
15	dorzolamide.mp.	1176
16	echothiophate.mp.	461
17	latanoprostene.mp.	57
18	levobunolol.mp. or Levobunolol/	309
19	netarsudil.mp.	138
20	tafluprost.mp.	280
21	bimatoprost.mp. or Bimatoprost/	903
22	tafluprost.mp.	280

23	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 or 19 or 20 or 21 or 22	134560
24	limit 23 to (english language and humans and yr="2018 -Current")	5096
25	limit 24 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	140

Appendix 3: Prescribing Information Highlights

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

OMLONTI® (omidenepag isopropyl ophthalmic solution) 0.002%, for topical ophthalmic use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------
Omlonti (omidenepag isopropyl ophthalmic solution) 0.002%, is a relatively selective prostaglandin E2 (EP2) receptor agonist, indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage is one drop in the affected eye(s) once daily in the evening. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.002% (0.02 mg/mL) of omidenepag isopropyl. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Pigmentation (5.1)
- Eyelash changes (5.2)
- Ocular Inflammation (5.3)
- Macular Edema (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions with incidence ≥ 1% are conjunctival hyperemia (9%), photophobia (5%), vision blurred (4%), dry eye (3%), instillation site pain (3%), eye pain (2%), ocular hyperemia (2%), punctate keratitis (2%), headache (2%), eye irritation (1%), and visual impairment (1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Santen at 1-855-7-SANTEN (855-772-6836) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Appendix 4: Key Inclusion Criteria

Population	People with open angle glaucoma and ocular hypertension
Intervention	Topical medications approved for the treatment of glaucoma and ocular hypertension
Comparator	Placebo or active treatments
Outcomes	Intraocular pressure reduction, visual field changes and withdrawals due to adverse events
Setting	Outpatient