Unoprostone isopropyl 0.15% Ophthalmic Solution (Rescula)

National PBM Drug Monograph

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions.  These documents will be updated when new data warrant additional formulary discussion.  Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Executive Summary**

* Unoprostone is a docosanoid, a structural analog of prostaglandin F2α. It does not have an affinity for prostaglandin receptors including the FP receptor. It is believed to reduce intraocular pressure by increasing outflow of aqueous humor through the trabecular meshwork
* Unoprostone is approved for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
* The recommended dose is one drop in affected eye(s) twice daily
* Comparative trials indicate that the intraocular pressure (IOP) lowering ability of unoprostone is less than latanoprost, timolol, and brimonidine when used as monotherapy. There was no significant difference in IOP lowering efficacy between unoprostone + timolol and treatments combining brimonidine or dorzolamide to timolol.
* Unoprostone has the following warnings/precautions similar to the prostaglandin analogues: increased pigmentation of the iris, eyelid, and eyelashes; eyelash changes (increased length, thickness, number); cautionary note on use in patients with active intraocular inflammation; reports of macular edema.
* The acquisition cost of unoprostone substantially exceeds that of the other formulary agents used to treat glaucoma.

**Introduction**

Unoprostone was originally approved in 2000 as a prostaglandin analog and a second-line agent for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive to another intraocular pressure lowering medication. However, it disappeared from the US market in the mid-2000s likely due to competition from the prostaglandin analogs offering greater IOP reduction and once-daily dosing.

In 2012, the FDA approved the supplemental new drug application to change the product labeling to include the indication as a first-line agent and to reclassify its drug class from a prostaglandin analog in the prostaglandin family, to a docosanoid in the prostone family. Unoprostone was re-launched in March 2013 by Sucampo which has commercialization rights for this product.

**Pharmacology**

Unoprostone is a docosanoid, a structural analog of prostaglandin F2α. It does not have an affinity for prostaglandin receptors including the FP receptor. It is believed to reduce intraocular pressure by increasing outflow of aqueous humor through the trabecular meshwork. The exact mechanism of action is unknown at this time; it may involve relaxation of the trabecular meshwork fibers by stimulating the BK (Big Potassium) channels and CIC-2 chloride channels.

**Pharmacokinetics**

* Absorbed through the cornea and conjunctival epithelium where it is hydrolyzed by esterases to the active metabolite, unoprostone free acid
* Minimal systemic absorption (mean peak concentration <1.5ng/mL)
* Little or no accumulation of unoprostone free acid
* Unoprostone free acid is further metabolized to several inactive metabolites
* Rapid elimination from plasma with half-life of 14 minutes; metabolites primarily excreted in the urine

**FDA Approved Indications**

For reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**Current VA Alternatives**

Topical agents: Latanoprost, timolol, betaxolol, levobunolol, brimonidine, dorzolamide, pilocarpine, carbachol, dorzolamide/timolol, brimonidine/brinzolamide

**Potential Off-Label Uses**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) (available on the VA PBM Intranet site only).

* Retinitis Pigmentosa (Patient enrollment for Phase 3 trial complete)
* Dry Age-related Macular Degeneration (Phase 2 trials complete)

**Dosage and Administration**

* The recommended dose is one drop in affected eye(s) twice daily
* If more than one topical ophthalmic product is being used, each one should be administered at least 5 minutes apart.
* Contact lenses are to be removed prior to application of unoprostone. Patients should wait 15 minutes before reinserting lenses

**How Supplied/Storage and Handling**

Unoprostone 0.15% solution is supplied as 5mL in a 7.5mL bottle

Preservative: Benzalkonium chloride 0.015%

Store between 2°-5°C (36°-77°F)

**Efficacy**

Seven trials (4 parallel and 3 cross-over) using the marketed strength of 0.15% are included (**Table 1**). In all trials, unoprostone was compared to an active comparator. Three trials were monotherapy and 3 were in combination with timolol 0.5%. The longest and largest trial was of 6 months duration and compared unoprostone to timolol and betaxolol as monotherapy. One trial was conducted in paired-eyes of patients with bilateral glaucoma or ocular hypertension. Intraocular pressure was the measured outcome in all trials.

*Monotherapy*

The trials by Sponsel et al. and Jampel et al. showed that reduction in IOP was significantly greater with latanoprost than unoprostone. In addition, 5 clinical trials comparing an earlier formulation of unoprostone 0.12% to latanoprost support that IOP lowering efficacy is significantly greater with latanoprost. In another trial, equivalence between unoprostone and timolol was not demonstrated; however, unoprostone was found to be equivalent to betaxolol. The study comparing unoprostone to brimonidine found the earlier IOP time points favoring brimonidine (10am and 12n) and the later IOP time points favoring unoprostone (4pm and 6pm). However, in this study, brimonidine, a drug typically dosed three times daily, was dosed q12hours which likely explains the waning effects noted later in the day.

*Combination with Timolol*

There was no significant difference in IOP lowering efficacy between unoprostone + timolol and treatments combining brimonidine or dorzolamide to timolol.

**Table 1: Phase 3 Trials**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Treatment Arms** | **Baseline IOP (mmHg)** | **Change in IOP (mmHg)** | **Summary** |
| **Nordmann 2002**R, DB, parallel6 months | UNOP 0.15% (n=278)TIM 0.5% (n=138)BETAX 0.5% (140) | **IOP early morning/mid-morning/noon/evening/diurnal**24.2/23.8/22.6/22.4/23.324.2/23.7/23.2/22.8/23.524.6/24.1/22.9/22.9/23.6 | **IOP early morning/mid-morning/noon/evening/diurnal**-4.4/-4.7/-4.3/-4.0/-4.3-6.0/-6.0/-5.9/-5.3/-5.8-4.6/-5.4/-5.0/-4.6/-4.9 | •UNOP was NOT  equivalent to TIM•UNOP was  equivalent to BETAX |
| **Sponsel 2002**R, evaluator-masked, bilateral eyes28 daysN=25 | UNOP 0.15%LAT 0.005% | **IOP 8am/4pm**19.5/18.318.8/17.6 | **IOP 8am/4pm**-1.6/-2.4-2.6/-3.1 | Significantly greater IOP ↓ with LAT vs. UNOP |
| **Jampel 2002**R, EM, parallel8 weeks | UNOP 0.15% (n=81)LAT 0.005% (n=84) | **IOP 8am/12n/4pm/pooled mean**27.3/24.8/24.3/25.527.1/25.1/23.9/25.3 | **IOP 8am/12n/4pm/pooled mean**-5.2/-3.2/-3.5/-3.9-8.3/-6.9/-6.3/-7.2 | Significantly greater IOP ↓ with LAT vs. UNOP |
| **Stewart 2004**R, CO,6-weeks/tx armN=35 | UNOP 0.15%BRIM 0.2% | **IOP 8am/10am/12n/2pm/4pm/****6pm/10pm/diurnal** 25.1/22.7/22.4/21/19.9/20.2/20/21.6 | **IOP 8am/10am/12n/2pm/4pm/****6pm/10pm/diurnal**-5.6/-3.8/-3.2/-2.8/-2.3/-1.9**^**/-1.5**^**/-3-5/-6.4\*/-4.7\*/-2.6/-1.8/-0.5/-0.6/-3.1 | ^Sig UNOP vs. BRIM\*Sig BRIM vs. UNOP |
| **Homer 2003**R,DB, parallel12 weeks | UNOP 0.15% + TIM 0.5% (n=50)BRIM 0.2% + TIM 0.5% (n=48)DORZOL 2% + TIM 0.5% (n=48) | Not shown | **8 hour diurnal IOP**-2.7-2.8-3.1 | No significant difference between UNOP and BRIM and DORZOL |
| **Day 2003**R, CO,6-weeks/tx armN=32 | UNOP 0.15% + TIM 0.5%DORZOL 2%/TIM 0.5% FDC | **IOP 8am/10am/4pm/6pm/8pm**24.3/23.8/23.2/22.9/23 | **IOP 8am/10am/4pm/6pm/8pm**-4.2/-4/-3.9/-3.4/-2.9-3.5/-4.7/-4.6/-3.2/-3.4 | No significant difference between treatment groups |
| **Sharpe 2005**R, CO,6-weeks/tx armN=33 | UNOP 0.15% + TIM 0.5%BRIM 0.2% + TIM 0.5% | **IOP 8am/10am/4pm/6pm/****10pm/diurnal**23.3/22/21.8/21.2/21.6/22 | **IOP 8am/10am/4pm/6pm/****10pm/diurnal**-2.3/-4.9/-2.5/-0.7/-2.8/-2.7-1.7/-3.6/-3.1/-0.8/-1.8/-2.2 | No significant difference between treatment groups |

Abbreviations: BETAX=betaxolol; BRIM=brimonidine; CO=cross-over; DB=double blind; DORZOL=dorzolamide; EM=evaluator masked; FDC=fixed-dose combination; IOP=intraocular pressure; LAT=latanoprost; R=randomized; TIM=timolol; UNOP=unoprostone

**Safety**

Commonly reported adverse events observed in the clinical trials are shown in **Table 2**.

**Table 2: Adverse Events with use of Unoprostone**

|  |  |  |
| --- | --- | --- |
| **Ocular AEs** | 10-25% of patients | Burning/stinging, burning/stinging upon instillation, dry eyes, itching, increased eyelash length, conjunctival injection |
| 5-10% of patients | Abnormal vision, eyelid disorder, foreign body sensation, lacrimation |
| 1-5% of patients | Blepharitis, cataract, conjunctivitis, corneal lesion, discharge from eye, eye hemorrhage, eye pain, keratitis, irritation, photophobia, and vitreous disorder |
| **Nonocular AEs** | ~6% of patients | Flu-like symptoms |
| 1-5% of patients | Accidental injury, allergic reaction, back pain, increased cough, diabetes mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, sinusitis |

Data obtained from product package insert

In the individual trials, the smaller cross-over trials showed no significant difference in adverse events between treatments. Adverse events reported in the larger parallel trials are shown in **Table 3**.

**Table 3: Adverse Events (%) Reported in Parallel Trials**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Nordmann** | **Jampel** | **Hommer** |
| **UNOP****N=278** | **TIM****N=138** | **BETAX****N=140** | **UNOP****N=81** | **LAT****N=84** | **UNOP+ TIM****N=50** | **BRIM + TIM****N=48** | **DORZ + TIM****N=48** |
| ≥ 1 AE | Not reported | 47 | 26 | 22 | 22.9 | 29.2 |
| Discontinued due to AE | 3.6 | 3.6 | 1.4 | Not reported | 6.0 | 4.0 | 6.2 |
| Burning/ stinging on instillation | 6.8 | 2.9 | 12.9 | - | - | 8.0 | 0 | 2.1 |
| Burning/stinging | 18 | 11.6 | 22.1 |  |  | 4.0 | 4.2 | 14.6 |
| Conjunctival hyperemia | 10.8 | 3.6 | 5.0 | 0 | 2.0 | - | - | - |
| Itching | 7.9 | 2.2 | 6.4 | - | - | 0 | 8.3 | 0 |
| Tearing | 2.5 | 1.4 | 5.0 |  |  | 2.0 | 2.1 | 4.2 |
| Dryness | - | - | - | 2.0 | 0 | - | - | - |
| Eyelid disorder | 5 | 3.6 | 5.7 |  |  | - | - | - |
| Blurred vision | 3.6 | 5.1 | 1.4 | 2 | 1 | - | - | - |
| Foreign body sensation | 3.2 | 1.4 | 7.1 | - | - | 4.0 | 4.2 | 0 |
| Eye pain | - | - | - | 15 | 1 | - | - | - |
| Eye irritation | - | - | - | 20 | 6 | - | - | - |

**Look-alike / Sound-alike (LASA) Error Risk Potential**

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

**Table 14: Results of LASA Search**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NME Drug Name** | **Lexi-Comp** | **First DataBank** | **ISMP** | **Clinical Judgment** |
| UnoprostoneRescula | NoneNone | NoneNone | NoneNone | Dinoprostone, Lubiprostone, MifepristoneRescriptor, Retisert, Acular |

**Contraindications**

Hypersensitivity to unoprostone or any other ingredient in the product

**Warning/Precautions**

Unoprostone has the following same warnings and precautions as the PGAs. Please refer to product package insert for further details

* Increased pigmentation of the iris, eyelid, and eyelashes
* Eyelash changes which may include increased length, color, thickness, shape and number of lashes
* Use with caution in patients with active intraocular inflammation (e.g., iritis, uveitis) because inflammation may be exacerbated
* Macular edema has been reported. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

**Drug Interactions**

None

**Pregnancy/Nursing**

Pregnancy Category C: In rat and rabbit studies, there were no teratogenic effects. There was an increase in the incidence of miscarriages and a decrease in live birth index when administered subcutaneously during organogenesis. When administered subcutaneously to rats during late gestation, there was an increase incidence of premature delivery, decrease in live birth index and decrease in weight at birth, and delayed growth.

Unoprostone should not be used during pregnancy unless the potential benefit justifies potential risk to the fetus.

Nursing: It is not known if unoprostone is excreted in human milk. Use caution if unoprostone is administered to nursing women.

**Cost**

Please refer to VA pricing sources for updated information.

**Conclusion**

Comparative trials indicate that the IOP lowering ability of unoprostone is less than latanoprost, timolol, and brimonidine when used as monotherapy. In combination trials with timolol, there was no significant difference between the addition of unoprostone, brimonidine, or dorzolamide. At this time, unoprostone should be reserved for patients who are unable to tolerate the formulary agents.

**References**

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Product package insert for Rescula November 2012

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