

Special Report) CONTEMPORARY SURGICAL & CLINICAL STRATEGIES IN **GLAUCOMA****CO₂ laser-assisted procedure showing long-term efficacy, safety**

Simplified filtration procedure has short learning curve; reduced need for topical drugs

By Cheryl Guttman Krader; Reviewed by Noa Geffen, MD, and Michael Mimouni, MD

TRAVATAN Z[®]
(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION**INDICATIONS AND USAGE**

TRAVATAN Z (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

TRAVATAN Z (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS**Pigmentation**

Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes

TRAVATAN Z Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

TRAVATAN Z Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z Solution should be used with caution in aphakic patients, in pseudophakic patients with a tor posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma

TRAVATAN Z Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses

Contact lenses should be removed prior to instillation of TRAVATAN Z Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS**Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z (travoprost ophthalmic solution) 0.004% and TRAVATAN Z (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN Z or TRAVATAN Z Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS**Pregnancy****Pregnancy Category C**

Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z Solution is administered to a nursing woman.

Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and Renal Impairment

Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day (250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)). At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION**Potential for Pigmentation**

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z Solution.

Use with Contact Lenses

Contact lenses should be removed prior to instillation of TRAVATAN Z Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only

U.S. Patent Nos. 5,631,287; 5,889,052; 6,011,062; 6,235,781; 6,503,497; and 6,849,253

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TEL AVIV, ISRAEL ::

CO₂ LASER-ASSISTED sclerectomy (CLASS, IOptima) is a safe technique providing long-term IOP control with a reduced need for topical medications, show findings from follow-up to 5 years in a multinational trial.

"We are fortunate to be caring for patients in an era of glaucoma surgical innovation, and



Dr. Mimouni

newer microinvasive procedures offer benefits in terms of their safety profiles," said Michael Mimouni, MD, Department of Ophthalmology, Rambam Health Care Campus, Haifa, Israel. "However most do not provide adequate IOP

control over time in eyes with more advanced glaucoma."

CLASS, developed by Professor Ehud Assia, MD, Department of Ophthalmology, Meir Medical Center, Kfar-Saba, Israel, is a simplified filtration procedure that has a short learning curve.

Outcomes from the studies published by Noa Geffen, MD, principal investigator, and the international CLASS group, show that it can be performed with repeatable efficacy and safety in the hands of different surgeons, Dr. Mimouni noted.

"Now we look forward to confirming these promising results with more data," he said.

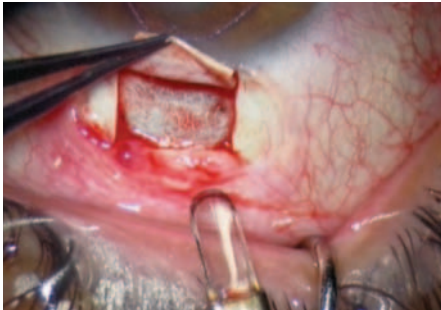
MORE ABOUT CLASS

CLASS is performed with a proprietary laser system (IOptiMate, IOptima) that includes a 10.6 μm CO₂ laser, a control unit, and a micro-manipulating scanner integrated with the surgical microscope.

After creating a peritomy and half-thickness scleral flap, the laser is used to ablate the zone directly above Schlemm's canal in order to achieve deep scleral ablation and unroofing of Schlemm's canal. The laser ablates tissue layer by layer until percolation of fluid is visualized.

CLASS requires a manual creation of a partial thickness scleral flap but overcomes the need to manually create the deeper flap,

WATCH THE PROCEDURE



VIDEO The CLASS procedure is highly efficacious, with minimal learning curve. (Video courtesy of IOPTima)
Go to <http://bit.ly/2aw5iQb>

which is the more challenging step in the standard non-penetrating deep sclerectomy procedures.

“The CO₂ laser was chosen for this procedure because its wavelength effectively ablates dry tissue, but is highly absorbed by water,” Dr. Mimouni said. “The laser is used to ablate the deeper scleral layer until percolation is achieved, without perforation.”

STUDY RESULTS

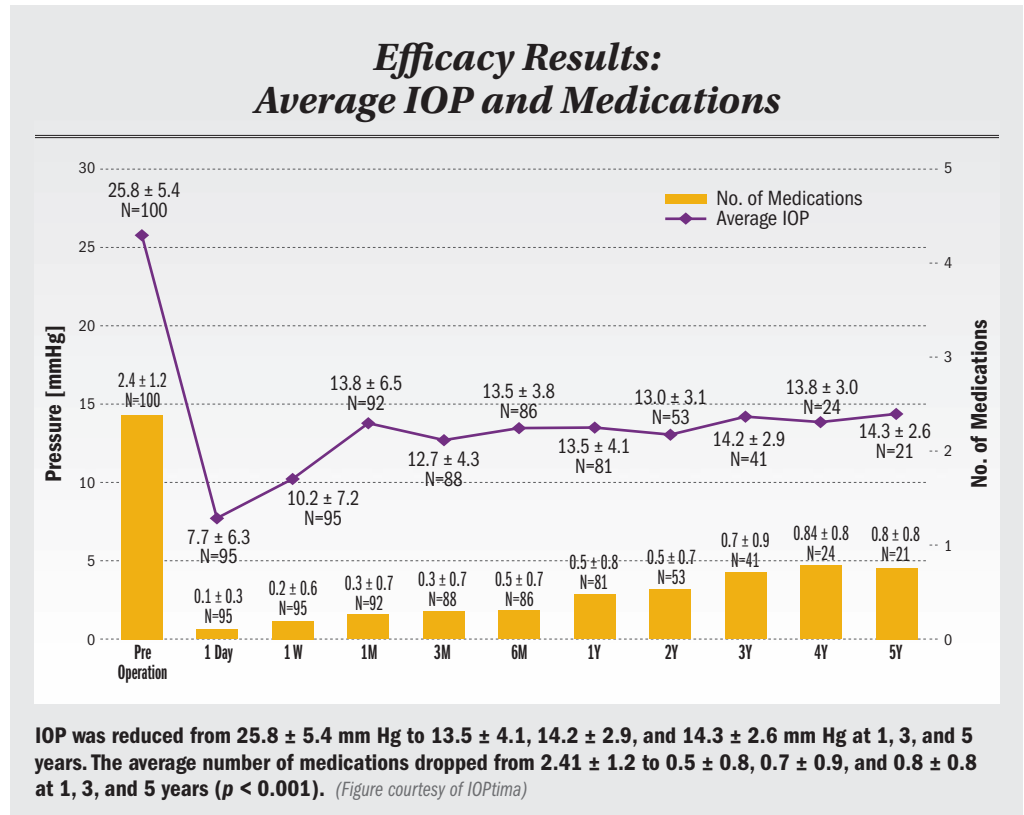
The multinational prospective study enrolled patients at nine sites in seven countries across three continents. It followed earlier testing in animal models showing that CLASS could be performed without causing perforation [Ton Y, et al. *J Glaucoma*. 2012;21:135-140] and after achieving positive results in an initial clinical trial including 37 eyes [Geffen N, et al. *J Glaucoma*. 2012;21:193-198].

Patients were eligible for study participation if they had primary open-angle glaucoma or primary exfoliation glaucoma with an IOP

‘The laser is used to ablate the deeper scleral layer until percolation is achieved.’

– Michael Mimouni, MD

>18 mm Hg despite maximum tolerated medical therapy, Shaffer angle >grade 2, no ocular disorders other than cataract, and no surgical intervention in the study eye other than clear



corneal cataract surgery. About three-fourths of the study participants had primary open-angle glaucoma.

Mitomycin-C was used in 89% of procedures. During the first year after the laser treatment, there were 12 needling procedures and 18 goniopunctures.

Efficacy results analyzed data from 100 eyes, of which 81 were seen at 1 year, 41 at 3 years, and 21 at 5 years. Mean IOP was 25.8 ± 5.4 mm Hg at baseline, 7.7 ± 9.5 mm Hg on the first day after surgery and averaged 13.5 ± 4.1, 14.2 ± 2.9, and 14.3 ± 2.6 mm Hg at 1, 3, and 5 years, respectively.

Prior to CLASS, patients were on an average of 2.4 ± 1.2 medications daily, and the average number was reduced significantly to 0.5 ± 0.8, 0.7 ± 0.9, and 0.8 ± 0.8 at 1, 3, and 5 years, respectively.

Complete success, defined as IOP between 5 and 18 mm Hg with a ≥20% reduction from baseline on no medications, was achieved in 59.1% of eyes seen at 1 year, 43.5% at 3 years, and in 40.9% of eyes followed to 5 years.

Qualified success, which was defined using the same IOP criteria but with or without medication, was achieved at rates

of 78.5%, 84.8%, and 86.4% at 1, 3, and 5 years, respectively.

Complications were mostly mild without any significant sequelae. The most common procedure-related complications were early wound leak (8.3%), shallow anterior chamber (5.6%), and hyphema (4.6%).

“Although some of the patients experienced complications during follow-up, most were transient and mild,” Dr. Mimouni said. “In addition, they compared favorably with trabeculectomy if we consider the trabeculectomy arm of the Tube versus Trabeculectomy

Study in which 87% of eyes developed at least one complication by 5 years.” ■

take-home

► CO₂ laser-assisted sclerectomy performed with a proprietary laser system is a simplified filtration procedure that is showing good IOP-lowering efficacy and safety in eyes followed to 5 years.

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