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Purpose: The objective of the study was to review diurnal IOP control and its impact on sight preservation.

Methods: This is a retrospective study used in patients with elevated IOP. Patient IOPs were measured every 4 hours over a 24-hour period. Qualified patients provided open-label TRAVATAN® to dose once a day for 2 weeks. Following 2 weeks of dosing, IOP measurements were taken every 4 hours for 36 hours. Additional IOP measurements were taken at 60 and 84 hours after the last dose of TRAVATAN®.

Results: The IOP changes from baseline were statistically significant ($p \leq 0.0001$) at all time points out to 36 hours. Even without additional dosing, substantial IOP reductions (6 mm Hg) were maintained out to 84 hours.

Conclusions: Use of TRAVATAN® may have less impact on IOP maintenance due to non-compliance and missed doses. This could help prevent glaucomatous loss and preserve sight.

IMPACT OF INTRAOCULAR PRESSURE

MAINTENANCE ON SIGHT

PRESERVATION

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IMPACT OF INTRAOCULAR PRESSURE MAINTENANCE ON SIGHT PRESERVATION

THESIS

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By

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CHAPTER I

GLAUCOMA

Background of Glaucoma

Glaucoma is one of the leading causes of blindness and is a public health concern. Glaucoma may account for 13% of new blindness registrations each year (Fraser, 2001). Thylefors (1998, p. 90) estimated "that there are 7 million new cases of blindness each year." However, this estimation is not based solely on glaucoma.

Damage to the optic nerve is caused by intraocular pressure due to glaucoma (Anderson, 1989). Patients who become blind from glaucoma may not seek treatment until they are blind, as this disease does not exhibit any symptoms (Grant, 1982). The need for early diagnosis is imperative to prevent blindness. However, Fraser (2001, p.642) states, "Early detection of glaucoma is clearly desirable, but the means to achieve this on a population basis remains problematic."

Approximately 66.8 million people around the world have open-angle glaucoma. There are a few risk factors to keep in mind when assessing open-angle glaucoma. Some of these factors include age, race, family history, diabetes, hypothyroidism, elevated intraocular pressure (IOP), and optic nerve head cupping (Shields, 1997 & Kalluar, 2001).

Prevalence of vision loss and blindness does increase due to age (Muñoz, 2000). Lichter (1984, p. 18) indicates that the "prevalence of glaucoma goes up with each

decade of life, to the point where 7%-10% of people in their 70s and 80s have glaucoma." Therefore, age is a primary factor for glaucoma. Individuals aged 40-49 have a 0.22% chance of being diagnosed with glaucoma and this increases to 14.29% for those 80 years of age or older (Shields, 1997).

Race is a risk factor for open-angle glaucoma. It has been found that blacks develop glaucoma more frequently, more severely, and at a younger age than other races (Lichter, 1984). African-Americans are more likely to develop glaucoma than non-African-Americans ($p=0.006$) (Muñoz, 2000). The Baltimore Eye Survey showed that "blacks had higher rates of POAG [primary open-angle glaucoma] than whites at every age, with an overall age-adjusted relative prevalence of 4.3 based on the adjusted rates" (Tielsch, 1991, p. 373). A study conducted in Chicago, IL and found that there is a higher incidence of open-angle glaucoma in the black population (Wilensky, 1978).

Heredity is another risk factor to consider for the development of glaucoma. Family history prevalence is higher for patients diagnosed with glaucoma than those who do not have glaucoma (Budde, 2000). An associated gene has been identified for open-angle glaucoma. This gene is located in the *CLC1A* region on chromosome 1 and is the *MYOC/TIGR* (Budde, 2000 & Stone, 1997). Stone's study "suggests that mutations in *CLC1A* cause glaucoma in nearly 100,000 individuals in the United States" (Stone, 1997, p. 670). If an adequate screening tool can be developed to identify this gene, then appropriate therapy can be assigned before vision is lost.

As stated in the NEI publication *Facts About Glaucoma*, "Although you will never be cured of glaucoma, treatment often can control it. This makes early diagnosis

and treatment important to protect your sight" (NEI, n.d., p. 3). Therefore, it is important to understand who is at risk and how to detect glaucoma.

Etiology of Glaucoma

Glaucoma may be classified into two types: primary and secondary. Aqueous outflow obstruction and elevated IOP may cause the primary type of glaucoma (e.g., open-angle glaucoma). The primary glaucomas are not affiliated with other systemic or ocular conditions and are restricted to the anterior chamber (Shields, 1997). The secondary type of glaucoma (e.g., pigmentary glaucoma) may develop due to other systemic or ocular conditions that restrict aqueous outflow in an open anterior chamber (Kallaur, 2001).

Open-angle glaucoma is diagnosed through IOP measurements, visual field loss, and optic nerve damage (Coleman, 1999). However, "increased eye pressures are no longer included in the definitions of glaucoma, the reduction of eye pressures remains the mainstay of POAG treatment" (Coleman, 1999, p. 1803).

Health Problem

Loss of vision impacts the quality of life of individuals, especially if the vision loss can be prevented. Healthy Vision 2010, which is part of the Healthy People 2010 program, has been implemented. Healthy People 2010 is sponsored by the Department of Health and Human Services (HHS), which includes the National Eye Institute (NEI) and National Institutes of Health (NIH).

The goal of Healthy Vision 2010 is to improve quality of life and increase longevity. Healthy Vision 2010 will also try to stop health disparities. The program focuses on eye examinations and screenings for all ages, specific eye diseases (such as glaucoma, cataracts, and diabetic eye diseases), injury prevention, and vision rehabilitation.

To assist with the prevention of vision loss, Medicare will cover the cost of annual dilated eye examinations for people at risk for glaucoma (NIH, 2002). "HHS Secretary Tommy G. Thompson stated, 'Preventative benefits, such as this new glaucoma coverage, help keep people enrolled in Medicare healthy and improve their quality of life'" (NIH, 2002, p. 1).

The lower socioeconomic group is at highest risk of developing glaucoma or other preventable diseases; however, they are least likely to be covered by health insurance (Woolhandler, 1988). The racial differences seen with the prevalence of glaucoma may be due to social and economic factors as well (Javitt, 1991).

Medical therapy is used to control IOP. However, the cost is prohibitive to some patients and the cost is expected to rise. The total drug expenditures in 1996 were 62 billion of which $3.18 billion were ophthalmic drug sales. It was estimated that by 1997, $1 billion will be spent only on glaucoma medications (Vold, 2000).

However, with the use of medical therapy to reduce and maintain low IOP, the cost has to include the price of the medication, additional physician visits, and potential side-effects of the medication. Newly developed medications are more effective, better

tolerated, and better dosing regimen (Fiscella, 1999). These factors can influence patient compliance with the medication, thus impact IOP maintenance.

Health-care professionals (e.g., ophthalmologists) use IOP measurements as an indicator for glaucoma management. "There is a definite causal relationship between the level of IOP and damages of the optic nerve head with resultant changes of the visual field in glaucoma" (Kitazawa, 1975, p. 557). Each physician makes a decision based upon a target IOP for each individual patient despite optic disc and visual field defects to begin pharmaceutical treatment (Shields, 1997). However, there exist little criteria for determining the target IOP for individual patients (Mao, 1991).

IOP should be measured throughout the day to ascertain the peak and trough pressures. Single measurements may not represent the diurnal cycle (Wilensky, 1993). To capture the diurnal curve, IOP must be measured periodically through a 24-hour cycle. The peak diurnal variation may occur at anytime; however, the usual peak time occurs between 6:00 a.m. and 8:00 a.m. (Phelps, 1974).

Glaucoma diagnosis and management may be affected by IOP, which should be measured at various times throughout the day (David, 1992). A single IOP measurement does not provide adequate information on IOP range and variability (Wilensky, 1993). Therefore, IOP must be measured throughout the day to assess an individual patients target pressure (Asrani, 2000).

Treatment is focused on lowering IOP as there is not a treatment available for optic neuropathy (Alward, 1998). The first choice of most health-care professionals in lowering IOP is a nonselective beta-adrenergic blocking agents such as TIMOPTIC®

(timolol ophthalmic solution, 0.25% or 0.5%). Prostaglandin analogues are a new class of agents used in the treatment of open-angle glaucoma and ocular hypertension. The new prostaglandin analogues are as effective as TIMOPTIC® but do not have the adverse systemic side-effects (such as bronchospasm or arrhythmia) of the nonselective beta-adrenergics (Netland, 2001).

Alcon Research, Ltd. has developed a prostaglandin analogue product, TRAVATAN® (travoprost ophthalmic solution, 0.004%), that was approved in March 2001 by the US Food and Drug Administration (FDA). The use of TRAVATAN® over a 24-hour diurnal cycle may help maintain target IOP and thus protect sight.

In summary, elevated IOP is an indicator of optic nerve head damage and visual field loss, which can lead to blindness. IOP reduction and IOP maintenance through medical therapy is an avenue for health-care professionals to treat glaucoma patients (Wilensky, 1991). When glaucoma is diagnosed early and treated, patients may preserve sight and prevent vision loss (Alward, 1998).

CHAPTER II

METHODOLOGY

Clinical Trials

Before clinical research trials are initiated in humans, a compound must be studied extensively. This preliminary research is conducted through pre-clinical (or laboratory) and animal testing. If the compound is found to have potential qualities for further studies, an Investigational New Drug Application (IND) is filed with the US Food and Drug Administration (FDA).

Clinical research has several phases, which include Phase I, Phase II, and Phase III. Phase I research is the initial use of the study drug in normal healthy volunteers to assess the safety profile of the product. Phase II of the research process begins the process of assessing efficacy of the product in the target population. Phase III studies are very large clinical trials that are conducted to provide additional information on the safety and efficacy of the study drug.

If the Phase III studies are successful, a New Drug Application (NDA) may be filed with the FDA. The product may be marketed after the FDA grants approval.

Further studies may be conducted on the product after approval. These additional studies are termed Phase IV studies (or post-marketing trials). These studies are used to help position the product on the market against the competition (CenterWatch, n.d.).

Also, these market support studies expose more patients to the drug product to gain additional efficacy information in the target population.

Volunteers are asked to participate in these clinical research trials. An Institutional Review Board (IRB) governs these research studies. The IRB is responsible for monitoring the clinical trial and protecting the rights and safety of the study participants. "All institutions that conduct or support biomedical research involving people must, by federal regulation, have an IRB that initially approves and periodically reviews the research" (ClinicalTrials.gov, n.d., p. 2).

A volunteer is asked to read and sign an informed consent document before agreeing to participate in a clinical research study. This document is designed to inform the volunteer about the study. The FDA has required information to be disclosed to the potential participant. "FDA requires that volunteers be told:

- that the study involves research of an unproven drug or device
- the purpose of the research
- how long the study is expected to take
- what will go on in the study and which parts of the study are experimental
- possible risks or discomforts
- possible benefits
- other procedures or treatments that you might want to consider instead of the treatment being studied
- that FDA may inspect study records, but the records will be kept confidential

- whether any medical treatments are available if you are hurt, what those treatments are, where they can be found, and who will pay for treatment
- the person to contact with questions about the study, your rights, and injuries related to research
- being in the study is voluntary and you can quit at any time" (US Food and Drug Administration, n.d., p. 1).

The informed consent document is reviewed and approved by an IRB. An example of the informed consent used in the Alcon sponsored study may be found in Appendix A.

The Alcon study used in this project was a Phase IV study to help position TRAVATAN® in the market. The TRAVATAN® package insert, which was approved by the FDA and gives pertinent information regarding the medication, is located in Appendix B.

There are several regulations and guidelines that were followed to protect human subjects and to adhere to Good Clinical Practice (GCP). These include Alcon Standard Operating Procedures (SOPs), Declaration of Helsinki, Code of Federal Regulations (21 CFR parts 50, 54, 56, 312, & 314), and International Conference of Harmonization (ICH) Guidelines (E6). The CFR and ICH Guidelines may be viewed on the world wide web at these locations: http://www.access.gpo.gov/nara/cfr/ and http://www.ifpma.org/ich1bis.html respectively.

Study Design

This is a research trial of TRAVATAN® (Travoprost Ophthalmic Solution 0.004%) used in patients with elevated intraocular pressure (IOP) conducted by the

Clayton Eye Center of Morrow, GA. Alcon Research, Ltd. sponsored the study. The objective of the study was to review diurnal intraocular pressure (IOP) control and its impact on sight preservation.

The study conducted by Alcon Research, Ltd. used commercial open-label TRAVATAN® without a comparison group. Subjects dosed once daily for two weeks at 8 p.m. in each eye. IOP measurements were collected every four hours up to thirty-six hours after dosing and out to eighty-four hours post dose. The Alcon Biostatistics Department analyzed the results following the Biostatistics Efficacy Analysis Plan.

The primary efficacy variable was IOP. A one-way analysis of variance was used to test the significance of mean change from baseline in IOP. Demographics were collected that included age, sex, race, iris color, and glaucoma diagnosis. Safety parameters included cardiovascular (resting pulse, systolic & diastolic blood pressure), ocular signs (cornea, iris/anterior chamber, lens), logMAR visual acuity, dilated fundus examination (retina/macula/choroid, optic nerve, vitreous, cup/disc ratio), and change in concomitant medication as a result of an untoward (unfavorable and unintended) event.

The original study was filed to the US Food and Drug Administration on the Investigational New Drug (IND) Application #51,000. The protocol, amendment #1, investigator, and informed consent were reviewed and approved by Sterling Institutional Review Board based in Atlanta, GA.

The study was divided into two phases. Phase I was the Screening/Eligibility Phase, which includes the Screening Visit, followed by the Eligibility Visit. Phase II was

the open-label treatment phase, which includes the Week 2 Visit, Week 2 + 2 day Visit, and Week 2 + 3 day Visit.

The subjects were consented and screened for the study at Clayton Eye Center. Based upon the inclusion and exclusion criteria, qualified subjects were enrolled into the study. Subjects had baseline IOP measurements conducted every four hours beginning at 8 a.m. over a twenty-four hour period after appropriate washout of their current glaucoma medication(s). The qualifying IOPs were 24 to 36 mm Hg at 8 a.m. and 21 to 36 mm Hg at 12 p.m. (noon) in at least one eye but the same eye must qualify at each time point. Neither eye could be greater than 36 mm Hg. After qualification, subjects were provided open-label TRAVATAN® and were instructed to instill one drop into each eye once daily at 8 p.m. The subjects returned in two weeks for the next study visit.

During the Week 2 Visit, subjects had IOP measurements conducted every four hours out to thirty-six hours. The Week 2 + 2 Days Visit was conducted at sixty hours and Week 2 + 3 Days was conducted at eighty-four hours after the last dose of TRAVATAN®.

CHAPTER III

RESULTS

Study Results

Clayton Eye Center conducted the study from June 20, 2001 through August 7, 2001. Twenty-one subjects diagnosed with open-angle glaucoma were enrolled into the open-label TRAVATAN® study. The demographics of the study group are given in Table 1 below, which includes age, sex, race, iris color, and glaucoma diagnosis. The average age of the study group was 59.4 (± 12.0 standard deviation). The study group was predominantly white females.

Table 1
Demographics of Subjects

Demographic Parameter	Number of Subjects	Percentage of Subjects
Age:		
< 65 years	12	57.1
≥ 65 years	9	42.9
Sex:		
Male	7	33.3
Female	14	66.7
Race:		
Caucasian	14	66.7
Black	7	33.3
Iris Color:		
Brown	11	52.4
Hazel	5	23.8
Blue	5	23.8
Glaucoma Diagnosis:		
Open-angle glaucoma	21	100.0

The baseline IOP measurements (with standard deviations) are given in Table 2 for all time points. The 8 a.m. and 12 p.m. (noon) IOP measurements had to be 21 to 36 mm Hg and 24 to 36 mm Hg, respectively, to qualify for participation in the study. The 8 a.m. IOP measurement averaged 26.5 (± 2.22) and the 12 p.m. IOP measurement averaged 24.4 (± 2.60).

The on-therapy IOP measurements (with standard deviations) for all time points are given in Table 3 for the Week 2, Week 2 + 2 Days, and Week 2 + 3 Days study visits. The change from baseline for mean IOP measurements are calculated from the baseline IOP and the on-therapy IOP measurements. Twelve hours after the last dose of TRAVATAN® (8 a.m.), the IOP had the greatest change of –11.2 (± 2.79) mm Hg. Also, TRAVATAN maintained lower IOP out to eighty-four hours after the last dose [-6.6 (± 3.53) mm Hg]. Figure 1 gives a graphic representation of the mean IOP change from baseline.

Table 2
Baseline IOP Measurements

Time point	IOP	Standard deviation
8 a.m.	26.4	2.22
12 p.m. (noon)	24.4	2.60
4 p.m.	22.7	3.89
8 p.m.	21.4	2.20
12 a.m. (midnight)	19.6	2.54
4 a.m.	21.6	2.46

Table 3 Week 2, Week 2 + 2 Days, & Week 2 + 3 Days IOP Measurements			
Time point	Hour post-dose	IOP	Standard deviation
8 p.m.	0	13.2	2.72
12 a.m. (midnight)	4	15.3	3.45
4 a.m.	8	16.5	4.88
8 a.m.	12	14.8	3.62
12 p.m. (noon)	16	13.9	3.91
4 p.m.	20	13.0	2.61
8 p.m.	24	12.9	2.72
12 a.m. (midnight)	28	13.2	3.69
4 a.m.	32	17.1	4.43
8 a.m.	36	16.0	2.76
8 a.m.	60	19.0	4.49
8 a.m.	84	19.4	4.47

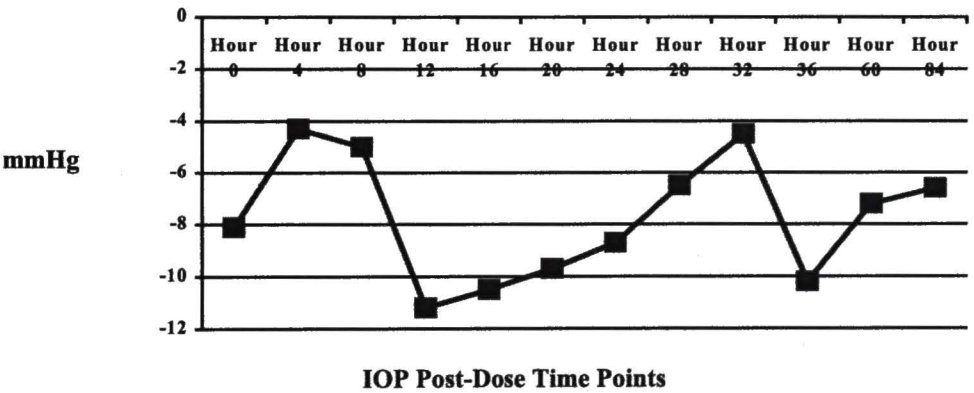

Figure 1
IOP Change from Baseline

Three subjects were excluded from the per-protocol efficacy data analysis for all visits due to inadequate washout of current glaucoma medication, less than thirty days of stable dosing with an anti-hypertensive medication, and use of an excluded concomitant

medication. One subject was excluded from the per-protocol efficacy data analysis at Week 2 8 p.m. (0 hour) Visit due to inadequate time interval from dosing with study medication to the IOP measurement.

Based upon these calculations it was determined that TRAVATAN® significantly lowered mean IOP at all time points ($p \leq 0.0001$) when measured over a thirty-six hour period after dosing (mean IOPs $\leq$ 17.1 mm Hg). The diurnally adjusted IOP changes from baseline were statistically significant ($p \leq 0.0001$) at all time points through thirty-six hours following the last dose of TRAVATAN®. Also, substantial IOP reductions (6 mm Hg) were maintained up to eighty-four hours without additional dosing. Therefore, patient non-compliance and missed doses may have less impact with use of TRAVATAN® on IOP control.

CHAPTER IV

CONCLUSIONS

Summary

"Glaucoma, a leading cause of irreversible vision loss in the United States, is a disease that affects three million Americans, half of whom do not know they have it because of its lack of early symptoms" (NEI, 2000, p. 1). There are some people at greater risk of developing glaucoma. "They include:

- Blacks over age 40.
- Everyone over age 60.
- People with a family history of glaucoma" (NEI, n.d., p. 1).

Glaucoma may be diagnosed through an eye examination. The use of IOP measurements, dilated examinations to view the optic nerve, and achromatic automated perimetry (e.g., visual field) are used to assess for glaucomatous damage. There are three common treatments for glaucoma 1) medications, 2) laser surgery, and 3) surgery (NEI, n.d.). Medications are usually the first line of treatment for glaucoma. When medications fail, then "laser energy applied to the trabecular meshwork (laser trabeculoplasty) may be used to increase aqueous outflow" (Alward, 1998, p. 1300). The last line of therapy for glaucoma is surgery.

Health Implications

Vision loss from glaucoma is irreversible; however, it can be controlled. The National Eye Institute has stated, "Eye disease, visual impairment and disability, and blindness are major public health problems" (NEI, 1994, p.1). "In addition to the physical and emotional stresses associated with eye disease and blindness, there are significant economic burdens. Eye disorders and blindness are estimated to cost the nation more than $16 billion annually" (NEI, 1994, p. 2). The National Eye Institute established the National Eye Health Education Program (NEHEP) after receiving funding in 1988 from Congress. "The goals of the NEHEP are to prevent vision loss and blindness by educating the public and health professionals about sight-threatening diseases" (NEI, 1994, p. 2).

Results Outcome

This was a very small (n = 21) clinical market support study of an Alcon product, TRAVATAN®. TRAVATAN® lowered IOP significantly at all time points out to thirty-six hours after the last dose ($p \leq 0.0001$). Even without additional dosing TRAVTAN® maintained substantial IOP reductions out to eighty-four hours (6 mm Hg).

The results from the study suggest that patients who use TRAVATAN® may have less impact on IOP maintenance due to non-compliance and missed doses. This would help prevent glaucomatous loss, which would lead to blindness, and preserve sight.

Health Impact

The diagnosis and management of glaucoma is very important to continued quality of life. According to Lee and Wilson (2000, p.91), "The diagnosis of glaucoma can affect quality of life in three major ways. These include the vision loss resulting from optic nerve damage, the various costs associated with its management, and the psychologic burden of carrying a disease that leads to progressive loss of vision."

Loss of sight can lead to decreased independence in performing daily activities, going places, and interacting with other individuals. The lack of independence caused by vision loss may lead to a feeling of "isolation, depression, and poorer social relationships" (NCHS, 2001, p. 1). "Visual impairment increases the risk of falls and fractures, making it more likely that an older person will be admitted to a hospital or nursing home, be disabled, or die prematurely" (NCHS, 2001, p. 2).

Over the next decade, $190 billion is proposed by the federal government to "modernize" Medicare (AARP, 2001). In January 2002, Medicare began covering dilated eye examinations to help detect glaucoma in high-risk groups (The Glaucoma Foundation, 2002). Early detection and treatment of glaucoma "could improve the quality of life for older people and decrease the level of disability" (NCHS, 2001, p. 7) for those with vision loss.

Therefore, continued efforts to diagnose and manage glaucoma are important in the continued quality of life of older persons. Use of topical medications, such as TRAVATAN®, help preserve the sight of those with glaucoma due to maintenance of IOP.

Appendix A

IRB Approved Subject Informed Consent

STUDY: Travatan ®
PROTOCOL: C-01-24
STERLING IRB ID: 1502 (AR 1014)
DATE OF IRB REVIEW: 8/21/01
DATE REVISED: 07/08/04

PARTICIPANT INFORMED CONSENT

STUDY TITLE: A Two-Week, Open Label Study of the IOP-Lowering Efficacy over a Twenty-Four Hour Period of TRAVATAN™ 0.004% Dosed Once Daily in Patients with Open-Angle Glaucoma or Ocular Hypertension

PROTOCOL NO.: C-01-24

STUDY DOCTOR: Harvey B. DuBiner, M.D.

STUDY SITE:

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Spalding Eye Center
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Best Western
380 Santa Rosa Blvd.
Ft. Walton Beach, FL 32548

Holiday Inn
200 S. Beachview Drive
Jekyll Island, GA 31527

TELEPHONE: 770-968-8888

SPONSOR: Alcon Research, Ltd.

INTRODUCTION:

The following information will describe this research study and your role as a research participant. Your eye doctor will answer any questions you may have about this Informed Consent Form and about this study. This Consent Form may contain words that you do not understand. Please ask your eye doctor (Investigator) or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form so that you will have time to think about and discuss this study with family or friends before making your decision.

Your eye doctor has identified you as having either open-angle glaucoma or ocular hypertension and has invited you to participate in an experimental eye research study. Open-angle glaucoma is an eye disease that produces abnormally high fluid pressure in the eye, called high intraocular pressure or high IOP. If untreated, this high pressure eventually causes damage to the eye and can cause blindness. Ocular hypertension is an eye condition in which the eye pressure is abnormally high, and is a risk factor for the development of glaucoma. Treatment for both open-angle glaucoma and ocular hypertension is aimed at lowering the eye pressure. Many glaucoma or ocular hypertension patients can control their high eye pressures with a drug placed into the eyes in the form of eye drops. There are several drugs approved by the United States Food and Drug Administration (FDA) and prescribed by doctors to treat glaucoma or ocular hypertension. The drug used in this study, TRAVATAN, is approved by the FDA for the treatment of these eye conditions.

The purpose of this research study is to determine the eye pressure lowering ability of TRAVATAN over a twenty-four hour period. Your doctor will allow you to participate in this research study if you are an adult patient at least 18 years of age and you meet other criteria that your doctor will explain to you. If you are eligible and you agree to participate in this study, you will be assigned to the

Participant's Initials_____

study drug, TRAVATAN. You will use the assigned medication once each day for two weeks. You will put one drop of the medicine into each eye in the evening at 8:00 p.m. You will remain on the study medication for two weeks. About 15 subjects will participate in this study.

In summary, your doctor has asked you to be in a eye research study. The purpose of this research is to study the ability of TRAVATAN to lower eye pressure over a twenty-four hour period in participants with open-angle glaucoma or ocular hypertension. You understand that one of the requirements to be in this study is that you must be an adult patient at least 18 years of age. You understand that there are other requirements that your eye doctor will explain to you.

PROCEDURES

Before you are accepted into this study, your doctor will examine you to make sure that you are free of certain illnesses. As a possible participant in the study, your doctor will ask you questions and you will undergo the following procedures:

The first visit, Screening Visit, will take place at either the Clayton Eye Center, or the Spalding Eye Center. On your first visit, the Screening Visit, your doctor will ask you to voluntarily sign an Informed Consent document. Your doctor will then ask you questions and examine you as a possible candidate for the study. Your doctor will record your medical history and, if you do not have any current or past medical conditions that will prevent your participation, your doctor will examine you. Your doctor will measure your blood pressure and pulse and will check your vision. Your doctor will examine your eyes with a microscope and measure the pressures inside your eyes. Your doctor will place drops into your eyes that will dilate them and enable your doctor to examine the back of your eyes with a microscope. Your doctor will perform a visual field test.

At the time of this Screening Visit, you will stop taking all of your current glaucoma eye drops or pills. If you are a female and you are capable of having children, you must not be pregnant or be planning to become pregnant during the study. You must not be nursing a baby and you must be using effective birth control (as determined by your doctor) at this time and continue using this birth control method throughout the study. You must have a pregnancy test with negative results before the start of the study.

Approximately one to four weeks after the Screening Visit, you will have an 24 hour Eligibility Visit with seven exams at 8:00 a.m., 12:00 p.m., 4:00 p.m., 8:00 p.m., 12:00 a.m., 4:00 a.m., and 8:00 a.m. The 24 hour Eligibility Visit will take place at a hotel. Your study doctor will arrange and pay for all transportation, hotel accommodations and meals for you while you are participating in the 24 hour Eligibility Visit. At the first 8:00 a.m. exam, your doctor will check your vision, examine your eyes with a microscope, and record your blood pressure and pulse. Your doctor will measure your eye pressures at all seven exam times. You understand that the pressure inside your eye must meet certain requirements before your doctor will allow you to continue in the study.

If you qualify for the study, your doctor will give you a bottle of eye medicine that you will use once each day for two weeks. You will not throw away any bottles of study medicine when they are empty and you will bring all of your bottles with you to each doctor visit.

Participant's Initials _____

You will put one drop of medicine into each eye every evening, at 8:00 p.m., for two weeks. You will be required to visit your doctor at 2 Weeks, 2 Weeks +2 days, and 2 Weeks +3 days, after you receive the eye drops. Your study doctor will arrange and pay for all transportation, hotel accommodations and meals for you while you are participating in the 2 Week study visit. The 2 Week study visit will have exams at 8:00 p.m., 12:00 a.m., 4:00 a.m., 8:00 a.m., 12:00 p.m., 4:00 p.m., 8:00 p.m., 12:00 a.m., 4:00 a.m., and 8:00 a.m. At the first 8:00 p.m. exam, your doctor will check your eye pressures and administer the normal evening eye drops. Also, you will return all full, partial, and empty bottles of your study medicine. Your doctor will measure your eye pressures at all remaining exam times.

The 2 Week + 2 days and 2 Week + 3 days visits will take place at either the Clayton Eye Center or the Spalding Eye Center. The 2 Week +2 days and 2 Week +3 days visits will have one exam at 8:00 a.m. At the 2 Week +2 days visit, your doctor will measure the pressures in your eyes. At the 2 Week +3 days visit your doctor will check your vision, examine your eyes with a microscope, measure the pressures in your eyes, and record your blood pressure and pulse. Your doctor will place drops into your eyes that will dilate them and enable your doctor to examine the back of your eyes with a microscope. If you are a female and are capable of having children, you will have a pregnancy test done.

You may choose to stop participating in this research study at any time during the study for any reason. Your doctor may also decide that you must stop participating before the end of the study. If you leave the study early, your doctor will perform the tests that he would normally perform at the end of the study.

SAFEGUARDS:

You must tell your eye doctor all of your past and present medical conditions and allergies that you are aware of and all drugs and medications that you are currently using. You will not participate in this study if you are allergic to any of the study medications or their components. If you wear contact lenses, you must remove your contact lenses while you are putting the study medication eye drops in your eyes and wait fifteen (15) minutes after putting in the eye drops before you re-insert your lenses. You will bring your glasses with you on the study days. Additionally, you must not have received therapy with an investigational drug within the last 30 days.

RISKS AND PRECAUTIONS:

The tests used in the examinations could cause some discomfort. The eye pressure test involves the placement of eye drops containing a small amount of local anesthetic into the eye. It is important that you do not rub your eyes for at least fifteen (15) minutes after the drops are put in the eye, since particles or dust in the eye might scratch the cornea and the numbing drop would temporarily mask the pain. Minor abrasion to the corneal surface may rarely occur when eye pressure is measured.

The eye drops put into your eye to dilate the pupil to facilitate a better view of the inside and back of the eye may cause your vision to be blurred for a few hours and may also cause you to be more sensitive to bright light until the medication wears off. During this time, you should protect your eyes from bright light (i.e., wear sunglasses outdoors) and you should not drive or perform any hazardous activity until your vision returns to normal.

Participant's Initials_____

There is a risk that your eye pressures will increase while you are on the study. If at any time your doctor feels that your eye pressures may endanger your health, then your doctor will ask you to stop participating in the study.

When using the study eye drops, you might experience side effects (adverse events).

SIDE EFFECTS WITH USE OF TRAVATAN

TRAVATAN has been reported to cause changes to pigmented tissue (iris of the eye). These changes may be permanent. TRAVATAN may gradually change eye color, increasing the amount of brown pigment in the iris. The long-term effects and the consequences of potential injury to the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to several years.

In TRAVATAN the most common side effect observed was ocular hyperemia (increased blood in the eye) in 35% to 50% of patients. Side effects reported at 5% to 10% included decreased visual acuity, eye discomfort, sensation of something in the eye, pain, and pruritus (itching). Those reported at 1% to 4% included, abnormal vision, blepharitis (inflammation of the eyelids), blurred vision, enlarged cells, conjunctivitis (pink eye), dry eye, eye disorder, flare (reddening of skin around the eye), iris discoloration, keratitis (inflammation of the cornea), lid margin crusting, photophobia (sensitivity to light), subconjunctival hemorrhage (bleeding in the membrane that surrounds the eyelid), and tearing.

In clinical research studies some side effects not related to the eye were reported. Effects reported at 1% to 5% were accidental injury, angina pectoris (chest pain), anxiety, arthritis, back pain, bradycardia (slow heart beat), bronchitis, chest pain, cold syndrome, depression, dyspepsia (upset stomach), gastrointestinal disorder, headache, hypercholesterolemia (high cholesterol), hypertension (high blood pressure), hypotension (low blood pressure), infection, pain, prostate disorder, sinusitis, urinary incontinence (inability to control urination), and urinary tract infection.

STUDY COMPLICATIONS AND COMPENSATION TO YOU:

Reimbursement for medical expenses that are a direct result of an adverse event resulting from your participation in this study is available from the Sponsor, Alcon Research, Ltd.

COSTS TO YOU:

If you agree to participate in the study, the medications and the eye care received during your participation will be paid for by Alcon Research, Ltd. and will not result in any cost to you. You or your insurance company will be responsible for the charges associated with all other medical care.

The study doctor will pay for all of your expenses associated with the 24 hour Eligibility visit and the 2 Week visit. This includes all costs for your transportation, hotel accommodations and all meals while you are participating in these two visits.

Participant's Initials____ . _____

COMPENSATION TO YOU:

You will receive payment for participation in this study to cover your travel and parking expenses. You will be paid for each completed visit ($25.00 for Screening, $50.00 for Eligibility, and $100.00 for Week 2) for a total compensation of $175.00. If you do not complete all of the visits, you will be paid for the visits completed.

BENEFITS:

If you agree to take part in this study, it is possible that you will not receive any direct medical benefit. We hope the information learned from this study will benefit other patients with glaucoma and ocular hypertension in the future.

ALTERNATIVE TREATMENTS:

You do not have to participate in this study to receive treatment for your condition. Alternative therapies for the treatment of glaucoma and ocular hypertension are available. This includes medical (eye drops and pills) and surgical (laser and intraocular) treatments. Rather than participate in this study, you may choose to be treated with alternative therapies. Please talk to your eye doctor about these and other options.

WITHDRAWAL FROM THE STUDY:

Your decision to participate in this research study is voluntary. If you refuse to participate in this study you will not incur penalty or loss of benefits to which you are otherwise entitled. Should you decide to participate and then later choose to stop, your decision to stop will not affect your legal rights or the quality of health care that you receive from your eye doctor. If your eye doctor feels that it is in your best interest to stop participating in the study, then you must do so immediately. You may be required to undergo an additional visit and examinations. If any medical condition develops, your eye doctor may choose to stop the use of the study medicine and provide alternative treatment. Your eye doctor, the Institutional Review Board, Regulatory Agencies, or Alcon may stop your participation in the study at any time, with or without your consent.

At the end of the study or if you stop participating in the study before completion, your eye doctor will prescribe appropriate treatment for your eye condition.

NEW FINDINGS:

Your eye doctor will inform you of any significant new findings that may relate to and may affect your willingness to continue in the study.

CONFIDENTIALITY:

Dr. DuBiner and Alcon Research, Ltd. will keep your medical records from this study. Your eye doctor will submit information from this study to Alcon, to the U.S. Food and Drug Administration, and to the Institutional Review Board. National Regulatory Authorities, auditors, members of the Institutional Review Board, or representatives of Alcon may inspect your study records at any time. Results of the study may be reported to any National Regulatory Agency and may be used in

Participant's Initials_____

scientific publications or presentations, but no personal details will be released. All persons with access to your personal medical records will keep this information confidential within the limits of the law. However, because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. By signing this informed consent you are authorizing access to your records.

QUESTIONS

You are to rely on your eye doctor for information regarding the nature and purpose of this research study and the possibility of complications and alternative therapies. Your eye doctor will give you sufficient opportunity and time to discuss this information. If you have any questions related to this study or if you experience any effects or injury during your participation in this research study, please contact Dr. DuBiner or his staff at (770) 987-8888.

If you have any questions about this research or your rights as a research subject, you may contact Dr. Sally P. Green, Chairman of Sterling Institutional Review Board at (770) 690-9491.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will receive a signed and dated copy of this consent form.

Participant's Initials_____

PARTICIPANT'S CONSENT:

I have read or had read to me and I understand the information provided in this consent form.

I have received answers to all of my questions.

I freely decide to participate in this research study.

I authorize the release of my medical records to National Regulatory Authorities, auditors, members of the Institutional Review Board, or representatives of Alcon.

By signing this consent form I have not waived any of the legal rights which I other wise would have as a subject in a research study.

Signature of Participant	Date
Signature of Person Explaining the Consent	Date
Signature of Participant's Legal Representative (if required)	Date
Signature of Witness (if required)	Date

Appendix B

TRAVATAN® Package Insert

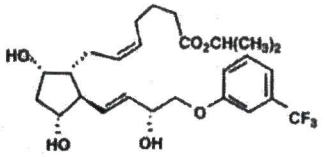
TRAVATAN®

(travoprost ophthalmic solution) 0.004%

Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.56. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN® Ophthalmic Solution 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN® 0.004% contains 40 µg travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive ingredients are: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

DM-00

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea. In humans, peak plasma concentrations of travoprost free acid (25 pg/mL or less) were reached within 30 minutes following topical ocular administration and was rapidly eliminated.

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α-carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Excretion: Elimination of travoprost free acid from human plasma is rapid. Plasma levels are below the limit of quantitation (<10 pg/mL) within one hour following ocular instillation.

Clinical Studies

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 - 27 mmHg who were treated with TRAVATAN® Ophthalmic Solution 0.004% dosed once-daily in the evening demonstrated 7 - 8 mmHg reductions in intraocular pressure. In subgroup analyses of these studies, mean IOP reduction in black patients was up to 1.8 mmHg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24 - 26 mmHg on TIMOPTIC® 0.5% BID who were treated with TRAVATAN® 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID demonstrated 6 - 7 mmHg reductions in intraocular pressure.

INDICATIONS AND USAGE

TRAVATAN® Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

WARNINGS

TRAVATAN® has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

TRAVATAN® may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of TRAVATAN®.

TRAVATAN® may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissues, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General

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 epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, gray-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation occurs.

TRAVATAN® should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® should be used with caution in these patients.

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

TRAVATAN® has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

TRAVATAN® Ophthalmic Solution should not be administered while wearing contact lenses.

Patients should be advised that TRAVATAN® contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®.

Since prostaglandins are biologically active and may be absorbed through the skin, women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and 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 µg/kg/day (250 times the maximum recommended human ocular dose of 0.04 µg/kg/day on a µg/kg basis (MRHOD)). At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 µg/kg/day (250 times the 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 µg/kg/day (75 times the MRHOD), and in mice at subcutaneous doses up to 1.0 µg/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 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses >-0.3 µg/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 the doses of ≥ 0.12 µg/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.

No adequate and well-controlled studies have been performed in pregnant women. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

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® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with TRAVATAN® 0.004% was ocular hyperemia which was reported in 35 to 50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

TRAVATAN® 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.

HOW SUPPLIED

TRAVATAN® (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's own DROP-TAINER® package system inside a sealed foil pouch.

TRAVATAN® is supplied as a 2.5 mL solution in a 3.5 mL, natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0266-25, 2.5 mL fill

Storage

Store between 2° - 25°C (36° - 77°F). Discard the container within 8 weeks of removing it from the sealed pouch.

Rx Only

U.S. Patent Nos. 5,631,287; 5,849,792; 6,096,662; 6,011,062; and 6,235,781

* TIMOPTIC is a registered trademark of Merck & Co., Inc.

Alcon®
PHARMACEUTICALS
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA


NDC 0065-0268-25
Rx Only
TRAVATAN
(travoprost ophthalmic solution) 0.004%
Alcon
2.5mL
Sterile
TRAVATAN

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