Off Label Uses of Common Medications

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Disclosure Statement:
Allergan Pharmaceuticals Speaker’s Bureau
Bio-Tissue
BioDLogics, LLC
Katena/IOP
Seed Biotech
Johnson and Johnson Vision Care, Inc.
Shire Pharmaceuticals

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- Live
- Immediate
- Accurate

Process of Approval

Company submits New Drug Application (NDA) to FDA
- Looking for safety and effectiveness for its intended purpose
- If application is approved
  - Indications
  - Contraindications
  - Dosage
  - Administration schedules

But......
- FDA does not have authority to regulate the practice of medicine

Off Label

Supplemental New Drug Application (SNDA)
- To apply for new indications
- Lag between submission and approval

WWW.AMAZON.COM $9.98
Statistics
- Literature indicates >50% of ophthalmic medications used off-label
- Annual US market for off-label medication use is $44 billion

Use of a medication or product for a different indication, age group, dosage or administration than approved by the FDA.

FDA Recommendations
- Good medical practice and the best interests of the patient require that physicians use legally available drugs according to their best knowledge and judgment

Off Label Use
- Responsible to be well-informed about product
- Base its use on firm scientific rationale and on sound medical evidence
- Maintain records of product’s use and effects

Xyrem (Orphan Medical)
- Indicated for the treatment of narcolepsy and to reduce cataplexy attacks
- Promotion of medication by pharmaceutical rep and physician
  - Caught on tape promoting its use for treatment of insomnia, fibromyalgia, restless leg syndrome, Parkinson’s disease, and multiple sclerosis, and in unauthorized patient populations

Orphan Medical and physician (Gleason) pled guilty
- Caronia was acquitted of misbranding, but convicted of conspiracy to introduce a misbranded drug into interstate commerce
- Orphan Medical was bought by Jazz Pharmaceuticals
- Caronia conviction overturned, citing 1st Amendment rights
  - Specifically, Caronia, a pharmaceutical sales representative, promoted the drug Xyrem for “off-label use,” that is, for a purpose not approved by the U.S. Food and Drug Administration (the “FDA”). Caronia argues that he was convicted for his speech -- for promoting an FDA-approved drug for off-label use -- in violation of his right of free speech under the First Amendment
- Gleason committed suicide
- Final FDA approval

Drug rep from Roche
Regional Manager wanted to boost declining sales
Encouraged rep to promote off-label use of Mycamine
  - Carolyn Gleason says she was ordered to market the drug for “all purposes” and to recommend dosages never approved by FDA

Xibrom was approved to treat pain and inflammation following cataract surgery
ISTA

- 2005-2010 ISTA employees promoted Xibrom for unapproved uses
- Following LASIK and glaucoma surgeries
- Treatment and prevention of CME
- Post-operative sheets for unapproved uses
- CME programs promoted unapproved uses
- Knowingly and willfully paid renumeration to physicians
  - Gave free Vitrase
  - Wine tasting
  - Golf outings
  - Payments to attend marketing sessions

Bottom Line

- Illegal for a drug company to introduce into interstate commerce any drug that the company intends will be used for purposes not approved by the Food and Drug Administration (FDA)
- $16,125,000 – criminal Fine
- $500,000 – conspiracy to violate Anti-Kickback Statue
- $1,850,000 – asset forfeiture
- $15,000,000 – to federal government
- ie $33.5 MILLION

ISTA resolution is part of the government emphasis on combating health care fraud
- Health Care Fraud and Prevention and Enforcement Action Team (HEAT)
- Since Jan 2009 $14.3 Billion recovered

Off Label Use

- Oral antibiotics
- Topical antibiotics
- Topical cyclosporine
- Topical corticosteroids
- Topical NSAIDs
- Topical anti-virals
- Others

Doxycycline Indications

Treatment of Susceptible Micro-organisms

- Rickettsiae
- Mycoplasma pneumoniae
- Agents of lymphogranuloma venereum
- Bartonella species
- Neisseria gonorrhoeae and Pasteurella tularensis
- Bartonella bacilliformis
- Bacteroides species
- Vibrio comma and Vibrio fetus
- Brucella species
- Cytophaga coli
- Enterobacter aerogenes
- Staphylococcus species
- Strep species
- Strep species and Neisseria species
- Haemophilis influenzae (respiratory infections)
- Haemophilis species (respiratory and urinary infections)
- H. ducreyi
- Neisseria gonorrhoeae and N. meningitis
- Treponema pallidum and Treponema pertenue
- Listeria monocytogenes
- Clostridium species
- Fusobacterium fusiforme
- Actinomyces species

- Only 2 FDA ophthalmic indications
Antibiotic vs. anti-inflammatory

Sub anti-microbial dose

Mechanism of Action
- reduce inflammation via anti-collagenolytic, anti-matrix-degrading metalloproteinase, and cytokine down-regulating properties

Ideal for Meibomian Gland Dysfunction
- Ability to accumulate in oil glands
- Regulates lipase
- The International Workshop on Meibomian Gland Dysfunction
- Tx with Doxycycline is late Stage 2 Tx or early 3

Other Uses-Recurrent Corneal Erosion

Matrix metalloproteinase (MMP)
- Name for group of enzymes that break down the structure of the extracellular matrix
- Gelatinase
  - Composed of MMP-9 and MMP-2
  - Degrades collagen type IV and VII and Laminin
  - all major components of BM

Elevated levels of MMP-9 and MMP-2 have been observed in tears of patients with RCE
- Higher levels of MMP may dissolve old and newly forming BM

Doxycycline inhibits MMP

Potential Side Effects
- Diarrhea
- Nausea
- Heartburn
- Headache
- Photosensitization (sunburn)
- Vaginal or oral candidosis
- Blood dyscrasias
- PTC
- Potentiate the effects of Coumadin

Contraindications
- Children under 8
- Depress bone growth
- Permanent tooth discoloration

Doxycycline shows 70% decrease in MMP activity in corneal cultures

Dosage may vary
- 20 mg to 50 mg BID

Treat for minimum of 2 months following RCE

Topical Antibiotics
- Ciloxan
- Vigamox/Moxeza
- Zymaxid
- Besivance
- Tobradex ST
- AzaSite
Indications

For the treatment of infections caused by the following microorganisms for the following conditions

- **Corneal Ulcers**
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Streptococcus pneumoniae*
  - *Streptococcus (Viridans Group)*
- **Bacterial Conjunctivitis**
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*

**Vigamox/Moxeza**

- moxifloxacin HCl 0.5%
- **Indications**
  - Treatment of bacterial conjunctivitis by susceptible organisms
- **Vigamox**: TID x 7 days
- **Moxeza**: BID x 7 days

**Zymaxid**

- gatifloxacin 0.5%
- **Indications**
  - Treatment of bacterial conjunctivitis by susceptible organisms
- **Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1**
- **Instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7**

**Besivance**

- besofloxacin 0.6% ophthalmic suspension
- **Indications**
  - Treatment of bacterial conjunctivitis by susceptible organisms
- **Developed specifically for topical ophthalmic use**
  - No widespread systemic, agriculture, or animal feed usage
  - Greatly reducing chance for resistance
  - Research shows some potential anti-inflammatory properties

**Off Label Uses**

- Corneal ulcers
- Corneal abrasions
- Empirical treatment of non-cultured ulcer
- Surgical prophylaxis of infection

**Other Uses- Interface Keratitis**

- Most sight threatening of interface disorders following LASIK
  - Rare but potentially devastating
  - Incidence:
    - Solomon et al 2003 – 0.03%
    - Moshirfar et al 2007 – 0.31%
    - Lovett et al 2010 – 0.035% (72 eyes of 204,586 from 2002-2008)
- Variety of organisms have been implicated
  - *Staphylococcus*
  - *Pseudomonas*
  - *Atypical mycobacteria*
  - *Fungi*
  - *Acanthamoeba*
  - *HSV*
  - *Adenovirus*
**Other Uses- Interface Keratitis**

- Most common non-viral cause of IK has evolved over time
  - Prior to 2005 Atypical Mycobacterium
  - Reduced incidence attributed to routine use of 4th generation fluoroquinolones

**Interface Keratitis**

- Most common non-viral cause of infectious keratitis has evolved over time
  - More recently Methicillin-resistant Staph aureus has become more common in early postoperative period
  - Due to potential to develop resistance to fluoroquinolones

**Interface Keratitis**

- Risk factors for IK
  - Blepharitis
  - Dry eye
  - Intraoperative epithelial defects
  - Excessive manipulation
  - Intraoperative contamination
  - Delayed postoperative re-epithelialization
  - Use of topical corticosteroids
  - Patients in health profession

**Interface Keratitis**

- Prevention
  - Infectious lid disease and dry eye treated pre-operatively
  - Intraoperative, strict adherence to aseptic techniques
    - Lid scrub with povidone-iodine solution
    - Use of different set of instruments for bilateral procedures
    - Ensure sterile water being used to clean instruments
  - Surgical prophylaxis

**AzaSite**

- AzaSite (Azithromycin 1%)

  **Indications**
  - for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms:
    - CDC coryneform group G, Haemophilus influenzae, Staphylococcus aureus, Streptococcus mitis group, Streptococcus pneumoniae
    - Broad-spectrum coverage against the most common gram-positive and gram-negative bacteria as well as atypical bacteria
  - Shows some resistance to gram-negative pathogens
  - Great for pediatric patients
  - Gel-forming drop

  **Dosage**
  - Instill 1 drop in the affected eye(s) twice daily for the first two days and then 1 drop in the affected eye(s) once daily for the next five days

**Off Label Uses-Azasite**

- [X]
**Off Label Uses- AzaSite**

- Meibomian gland dysfunction / Blepharitis
  - Chronic obstruction and inflammation of meibomian glands
  - Interferes with microbial protein synthesis
  - Prophylaxis for neonatal conjunctivitis

  - 2008 Clinical Trial
    - Divided into 2 groups
    - 1. Hot compresses twice daily x 10 minutes
    - 2. Hot compresses twice daily x 10 minutes
    - With 1 gtt BID OU x 2 days, then 1 gtt QD OU x 12 days

  - Results
    - 70% improvement in meibomian gland plugging vs. hot compresses alone
    - 44% of AzaSite users demonstrated no MG obstruction in at least 1 eye
    - 69% vs. 10% decrease in eyelid redness

  - The International Workshop on Meibomian Gland Dysfunction
    - Tx with Azithromycin is Stage 2 Tx

**Off Label Use- AzaSite**

- Recurrent Corneal Erosion
  - Inhibits MMP-9
  - BID x 2 weeks
  - QD x 1 month

  - Safety Profile
    - Pregnancy Category B
    - Indication for patients > 1 year old

  - Received stern warning letter in 2011 for Promotional material claiming “control ocular inflammation”

**Lotemax Gel**

- Indications
  - Corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

- Dosage
  - Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period.

- Contraindications
  - Contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures

**Lotemax Gel**

- Muco-adhesive technology

- Dose Uniformity

- Low preservatives with 2 known moisturizers

**Off Label Uses- Lotemax Gel**

- Allergies

- Iritis

- Herpes Zoster Keratitis

- Dry Eye
  - Induction therapy
  - Better penetration
  - QID x 2 weeks, then BID x 2-4 weeks
**Off Label Uses- Lotemax Ointment**

**Indications**
- Corticosteroid indicated for the treatment of postoperative inflammation and pain following ocular surgery

**Dosage**
- Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

**Atopic dermatitis**
- Caused by variety of allergic reactions and autoimmune diseases
- Contact with cosmetics, shampoos, hair care products

**Dry Eye**
- Induction therapy
- Complementary with Restasis
- QHS x 1 month

**Restasis**

**Indications**
- Topical immuno-modulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca

**Contraindications**
- In patients with known or suspected hypersensitivity to any of the ingredients in the formulation

**Dosage**
- 1 gtt in affected eye Q12H

**Inhibits activation of T-cell lymphocytes**
- T-cells play a central role in orchestrating various immune responses, including immunologic rejection of foreign tissue
- Has no impact on IOP, wound healing, viral replication
- Steroids?

**Vernal keratoconjunctivitis (VKC)**
- A seasonal form of allergic conjunctivitis
- Severe itching, redness, sensitivity to light, and discharge
- VKC has the potential to lead to corneal ulcers, keratoconus, and permanent vision loss
- Histopathological studies showed T-lymphocytes in the conjunctival papillae
- CD4+ subset of lymphocytes is known to produce IL-2

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Studies have proven that topical cyclosporine, with the correct formulation and concentration, will likely provide relief for both acute VKC and the recurrences of the disease. VKC may be a chronic condition that requires long-term anti-inflammatory treatment.

- Decreased symptoms (91%), decreased clinical signs (66%)

Herpes Stromal Keratitis
- Not active viral infection but viral antigens initiating a T-lymphocytic destruction of the stroma
- Studies show topical steroids effective
- Concerns?
  - May limit herpetic reactivation

Corneal transplantation
- Reduces inflammation, does not increase the susceptibility to infection
- Eliminates the issues surrounding the potential for a steroid response
- A study by Panda et al showed cyclosporine-treated grafts have been found to contain significantly fewer T-lymphocytes. This indicates that the topical cyclosporine actively inhibits the entry of T cells into the grafts, which may make it effective in reducing the risk of allograft rejection in high-risk patients.

Meibomian Gland Dysfunction
- Recurrent Corneal Erosions
  - Improves tear film
  - Controls MGD

Refractive Predictability Following LASIK

Topical cyclosporine A 0.05% for recurrent anterior uveitis
- Prabhu SS, Shtein RM, Michelotti MM, Cooney TM
- Poster Presentation ASCRS 2014

High-frequency Topical Cyclosporine 0.05% in the Treatment of Severe Dry Eye Refractory to Twice-daily Regimen
- Dastjerdi MH, Hamrah P, Dana R
Off Label Uses - Restasis

Bottom Line
- Topical cyclosporine is an excellent and safe alternative to topical corticosteroids
- Useful where patients may require long term or high dose topical steroids
- No impact on IOP or viral replication
- Does not slow wound healing or cause cataracts

Off Label Uses - Durezol

Diffuse Lamellar Keratitis (DLK)
- Interface inflammation following LASIK

Durezol (0.05% difluprednate)
- 2008 Approved for the treatment of inflammation and PAIN associated with ocular surgery
- First steroid to receive a specific indication that includes pain along with inflammation
- For the treatment of endogenous anterior uveitis 2012
- First potent steroid approved in more than 3 decades
- Originally developed for dermatology
- Original research was conducted in Japan and was compared to betamethasone
  - 6x more potent as an anti-inflammatory to PF
  - Found to be as potent, particularly when tx uveitis.

Xiidra

Any potential off label uses?
- Has anti-inflammatory properties
- Inhibits T-Cell recruitment and activation
- Another option when steroids may not be indicated

Durezol (0.05% difluprednate)
- Difluorinated derivate of prednisolone purposefully engineered to achieve max efficacy
  - 2 fluorine groups make more potent, other modifications
  - Increase drug penetration
  - Enhance anti-inflammatory activity
- Formulated as an emulsion for greater bioavailability
  - Provides consistent dosing, esp compared to PF
- No BAK, preserved in Sorbic Acid
- Dosed at half of PF
  - QIB as effective as Q2h PF

Off Label Uses - Durezol

Other uses
- Anterior segment surgery
- Glaucoma surgery
- Corneal grafting

Benefits
- More convenient dosing
- Higher potency

Watch IOP and side effects
Cystoid Macular Edema

Causes
- Medication side effects
- Trauma/injury
- Diabetes
- AMD
- Cataract surgery

Most common cause of decreased vision after cataract surgery

Higher risk patients

Durezol
- Very potent steroid with good penetrability
- Combine with NSAID

Has potential to increase IOP 5-6%, same as PF

PI SK

Secondary infections, cataracts

Cost prohibitive / accessibility

Not for every patient but good for:

Pregnancy Category C

Acular: indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of post-operative inflammation in patients who have undergone cataract extraction

Acular LS: indicated for the reduction of ocular pain and inflammation following corneal refractive surgery

Nevanac: indicated for the treatment of pain and inflammation associated with cataract surgery

Voltaren: indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery

Bromday: indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction

Prolensa: indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery

Ilevro: indicated for the treatment of pain and inflammation associated with cataract surgery

BromSite: indicated to prevent pain and treat inflammation in cataract surgery

81 year old AA female

Medical history: HTN

Ocular history: unremarkable

Unccomplicated cataract surgery

Uncorrected VA @ 3 months: 20/20 OD, OS

Returned two months later

BCVA 20/30 OD, 20/60 OS
Cystoid Macular Edema

- Most commonly seen after cataract surgery
- Described in 1953 by Irvine
- Angiographic CME after ICCE: As high as 60%
- Angiographic CME after ECCE: 15% to 30%
- Clinical CME after small incision phaco: 0.1%-2.35%
- OCT evidence of CME after small incision phaco: 4% to 11%
  - also reported to be as high as 41%

Cystoid Macular Edema

- Topical NSAIDs all approved for post-operative inflammation
  - But not specifically for CME
- Topical NSAIDs for prophylaxis
  - Wittpen at al (2008)
    - CME in 5 of 278 patients who received perioperative prednisolone, and in 0 of 278 who also received ketorolac
    - 450 patients
    - No cases of CME in patients treated with Nevanac and prednisolone
    - 5 cases of CME in group without Nevanac treatment

Cystoid Macular Edema

- Treatment
    - compared the efficacies of topical ketorolac, prednisolone and the combination of the two in 28 patients who developed CME within 21 to 90 days after cataract surgery
    - combination therapy resulted in superior visual acuity outcomes compared to monotherapies of either agent
    - those treated with a steroid/NSAID combination recovered from CME significantly faster than those who received no treatment

Off Label Uses-Topical NSAIDs

- Typically labeled for 2 weeks of post-operative use, starting treatment up to 1 day pre-operatively
- Commonly prescribed to start up to 3 days preoperative, with treatment continuing for 4 to 6 weeks in uncomplicated cases
- Prescribed off-label for prevention of CME

- Pain control
  - Corneal ulcers
  - Pterygium surgery
  - SLT

Off Label Uses-Topical NSAIDs

- Reducing inflammation associated with DES

- Reduction of pain following surface ablation
  - ketorolac only one approved
  - Studies with bromfenac
    - Sher NA, Golben MP, Bond W, Trattler WB, Tauber S, Voirin TG. Topical bromfenac 0.09% vs ketorolac 0.4% for the control of pain, photophobia, and discomfort following PRK. J Refract Surg. 2009;25:214-220.

Zirgan (0.15% ganciclovir ophthalmic gel)

- Approved 2009 for treatment of acute HSK or dendritic epitheliopathy
  - Has been avail in Europe since 1995
- First FDA approval for this class in 3 decades to help treat one of the 60k (29k pts) new cases of HSK each yr
  - 1 drop 5x/d (Q3H) until ulcer heals then TID for 7 d
  - no toxicity, very quick resolution, very comfortable
**Zirgan**

- Selectively inhibits synthesis of viral DNA
  - Competitive inhibition of viral DNA polymerase
  - Direct incorporation into DNA primer strand
- SE's
  - Blurred Vision (60%)
  - Irritation (20%)
  - SPK (5%)
  - Conj Hyperemia (5%)
- Pregnancy Category C
- Off label Tx of EKC
  - Safety not established below age of 2

**Epidemic Keratoconjunctivitis**

- Viral conjunctivitis caused by adenoviruses 8, 19
- Highly contagious
- Typically unilateral
- No sore throat / fever
- Redness
- Discomfort
- SEI
- Chemosis
- Photophobia

**Off Label Treatments- Zirgan**

- Research presented at ARVO 2001 by Tabarra et al.
  - 18 patients with EKC
  - Compared topical ganciclovir to preservative free tears
- Recovery Time | Presence of subepithelial opacities
---|---
Topical ganciclovir 0.15\% | 7.7 days | 22\%  
Preservative free artificial tears | 18.5 days | 77\%  

**Betadine (povidone iodine)**

- Topical Antimicrobial
- OTC
- Used to apply and clean wound or prep for Sx
- MOA
  - Oxidizes cell constituents
  - Iodinates proteins and inactivates them
- Side Effects
  - Severe pain on application
  - Irritation
  - Pruritic
  - Erythema
  - Edematous erythema

**Betadine**

- Helpful to Tx EKC
- There are no FDA-approved medicines to kill adenoviruses.
- But, an excellent off-label application of an FDA-approved drug is readily and inexpensively available:
  - 5\% Betadine Sterile Ophthalmic Prep Solution
- Decreases the viral load
  - PV entry into the anterior stroma stopping SEI
**Other Off Label Medications**

- **Avastin**
  - Initially approved to treat colorectal cancer
  - Expanded to lung cancer, metastatic breast cancer, glioblastomas, and metastatic renal cell carcinoma, cervical cancer, ovarian cancer
  - Inhibits VEGF
  - Study in 2008 at University of Wisconsin
  - Macular degeneration
  - Diabetic macular edema
  - IOP
  - Pre-surgical treatment for diabetic vitreous hemorrhage
  - Subconjunctival for corneal neovascularization

**Avastin**

- **Cystoid Macular Edema**

**Other Off Label Uses**

- **Prostaglandins**
  - Refractive fluctuations thought to be due to IOP
  - Minimal in intact cornea
  - Once daily dosing may stabilize or maintain IOP

- **Topical beta-blockers**
  - Passage of the beta-blockers into the nasal cavity and their rapid absorption into the blood vessels
  - Achieve therapeutic plasma levels within minutes
  - Delivery through the eyes is much quicker than through the gastrointestinal system

- **Exact MOA unknown**
  - Thought to be related to blocking the stimulating or activating effects of adrenalin

**Other Off Label Uses**

- **Alpha-agonists (Alphagan P)**
  - Post-surgical glare/halos (RK, LASIK, multi-focus implants)
  - Inhibits sphincter dilator muscle
  - Dosed 30-60 minutes before night time driving

**Other Off Label Uses**

- The recommended dosage is 1 drop of ALPHAGAN™ P 0.1% in the affected eye(s) 3 times daily, approximately 8 hours apart

  - *Dilute brimonidine to improve patient comfort and subconjunctival hemorrhage after LASIK*
Off Label Prescribing

- Increases our choices of medications
- Be prudent in decisions
- Be aware of potential side effects
- Make patient aware it is an off label treatment
- Consider consent form

SAMPLE CONSENT DOCUMENT TEMPLATE FOR DRUG OR DEVICE

When a drug or device is approved for medical use by the Food and Drug Administration (FDA), the manufacturer produces a "label" to explain its use. Once a device/medication is approved by the FDA, physicians may use it "off-label" for other purposes if they are well-informed about the product's uses or uses in firm, scientific method and sound medical evidence, and maintain records of its use and effects.

[State purpose of the off-label drug/device.]

[State alternatives to the off-label drug or device.]

[State known complications and side effects of the off-label drug/device.]

I understand that [state drug/device] was approved by the FDA for [state approval purpose/conditions]. Nevertheless, I wish to have [state treatment/procedure] performed on my eye/used in my eye and I am willing to accept the potential risks that my physician has discussed with me. I acknowledge that there may be other, unknown risks and that the long-term effects and risks of [state drug/device] are not known.

Thank You.

Please feel free to contact us:

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