

# EyeNet

 AMERICAN ACADEMY  
OF OPHTHALMOLOGY  
*The Eye M.D. Association*

# DISASTERS



## Be Prepared to Provide Care

UNDERSTANDING  
**Neurotrophic  
Keratopathy**

AMNIOTIC MEMBRANE:  
Breakthrough for  
**ACUTE STEVENS-JOHNSON**

**Optic Neuritis**

ONTT Data  
Discussed

DESTINATION  
**ATLANTA**  
Free Symposia



# Facing the Next **DISASTER**

## Preparedness for the Ophthalmologist

**Tornadoes lash a city, quakes collapse a bridge, floods burst a levee, explosions derail a commuter train.**  
**Is there a doctor in the house?**

**A** hurricane lays waste to New Orleans, a bomb blows up a London subway, a tsunami roils the Indian Ocean, a cyclone smashes Myanmar and earthquakes rumble through China.

Whether attributable to climate change, political terror or the increasing habitation of vulnerable geography, disasters around the world are on the rise in both frequency and severity.

On an almost daily basis a disaster, either natural or not, strikes somewhere in the world.<sup>1</sup> In 2007, the Federal Emergency Management Agency declared more than 60 major disasters in the United States alone, ranging from hurricanes, tornadoes and earthquakes to floods, fires and winter storms.<sup>2</sup> Although the statistics fluctuate from year to year, this figure is more than double the yearly average calculated since 1953.<sup>3</sup>

Complacency about making adequate preparations could leave you and your patients vulnerable to serious disruptions, if not dangerous situations.

**YOU NEED A PLAN** “You have to anticipate almost every eventuality. And you have to anticipate that what you expect may not actually occur; something entirely different may develop and you have to be ready,” said William J. Rand, MD, medical director at the Rand Eye Institute in Deerfield Beach, Fla. “You also have to make the assumption that local or fed-

eral help is not going to be on the way for some time, and you could be isolated for an extended period.”

**REMEMBER YOUR MEDICAL EDUCATION?** “The ophthalmologist also has to be prepared in some circumstances to become a general surgeon again,” said Henry L. Trattler, MD, in private practice at the Center for Excellence in Eye Care in Miami. “After Hurricane Andrew, I repaired many lacerations on the arms, legs and faces of patients, in addition to treating eye injuries. In disaster situations things may not go according to plan, and you just do what you have to do.”

Amy G. Coburn, MD, clinical associate professor of ophthalmology at Baylor College of Medicine in Houston, recalled an unexpected situation during which she helped care for more than 3,000 Katrina evacuees in Houston shelters: “We treated infections, lacerations and fractures, yet we also found that approximately 80 percent of the patients had refractive problems and important nonemergent issues, such as untreated glaucoma, cataracts and retinopathy. Many people were functionally impaired because they had lost their glasses and could not resume work or driving. We faced the problems of helping a displaced population more than a population with acute trauma.”



By Leslie Burling-Phillips, Contributing Writer

# SIX DEGREES OF PREPARATION

George Mills, senior engineer of the Standards Interpretation Group at the Joint Commission on Accreditation of Healthcare Organizations, outlined six areas to incorporate into an effective disaster plan:

**1. COMMUNICATION**—maintaining open lines both within an organization and externally to access community resources.

**2. RESOURCES AND ASSETS**—acquiring supplies, accessing community services, and understanding state and federal programs that help provide medical care in crises.

**3. SAFETY AND SECURITY**—maintaining a safe and secure environment for staff and patients.

**4. STAFF RESPONSIBILITIES**—adapt-

ing roles to meet unpredictable demands for patient care.

**5. UTILITIES MANAGEMENT**—ensuring the uninterrupted utilities during an emergency, including power, potable water and ventilation.

**6. PATIENT SUPPORT**—defining clear, reasonable plans to address the needs of patients during extreme conditions.

Identifying all the potential local hazards will optimize response efforts. This article details the JCAHO's points of preparation.

## 1. COMMUNICATION

Land-based communications that require power lines are not dependable in a large-scale disaster. So wireless technologies like cell phones and handheld radios become critical. "Although it's difficult to plan for all the potential contingencies, good communication during a disaster is essential. In an emergency, the directives and needs can change hundreds of times within an hour. You must be able to communicate with your suppliers, workers, physicians and others contributing to the response effort," explained Dr. Coburn.

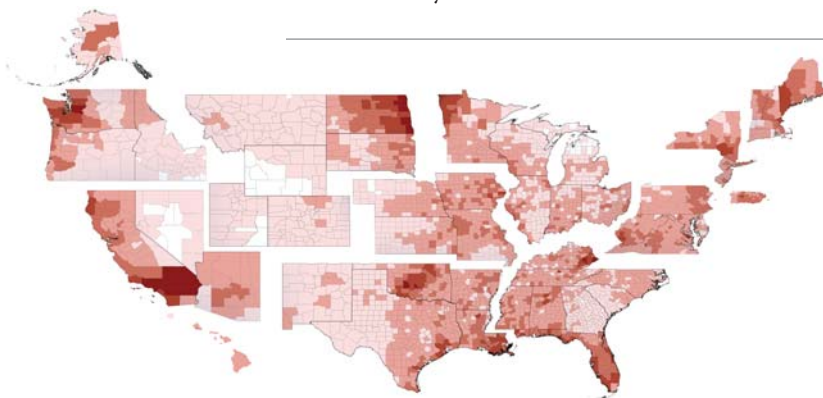
**TAKE CARE OF MRS. JONES.** Patients need to be communicated with, too. "All of our patients receive their doctor's home telephone number in case of an emergency. We do this year-round, not just during hurricane season. When a storm watch is announced, we try to reach all of our patients to make sure they have their medications. If someone

is elderly or infirm, we will send our vans on emergency distribution runs," said Dr. Rand.

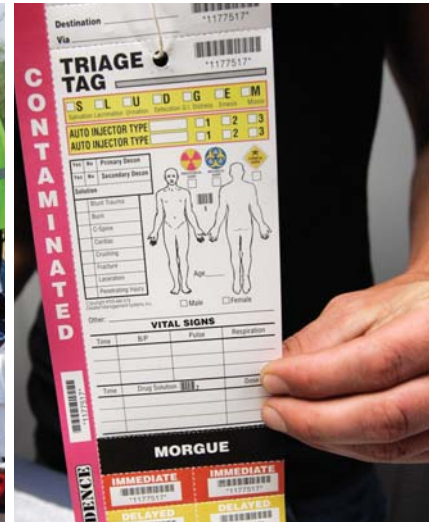
## 2. RESOURCES AND ASSETS

Many of those who will be assessing and treating patients after a disaster will be working within a hospital setting where medical supplies are typically stocked well in advance. "We stockpile a little bit of everything—dilating drops, antibiotics, surgical trays, instruments needed for minor procedures—essentially everything that we use on an ongoing basis. When a hurricane warning is announced, supplies are moved to a protected area so if we sustain substantial damage, we still have access to enough supplies to last for several weeks. We also store our diagnostic equipment and computers in rooms that do not have windows," said Erik van Kuijk, MD, PhD, professor of ophthalmology, vice chairman of clinical services and medical director of ophthalmology at the University of Texas in Galveston.

**DECIDE IF YOU WILL HELP.** Some practices may choose to be explicitly available in disasters. Designated an emergency critical care facility, the Rand Eye Institute is located adjacent to Broward General Hospital at North Broward Medical Center. "This is one of the first places people will come after a disaster. Items to provide immediate first aid are essential if you are going to be operational immediately after a disaster, which is our intention. Items such as gauze, Band-Aids, eye shields, eye pads and topical antibiotic ointments are available. Our emergency crash cart includes a defibrillator, IV tubing and solutions, catheters, first-line life support medications, cardiovascular medications and airway equipment, including oxygen, ambubags, oral airways, tracheal tubes and laryngoscopes. And, although it may never be used, a



From December 1964 to January 2008 FEMA recorded 1,550 disasters in the United States that were serious enough to warrant a presidential disaster declaration. FEMA tracks disaster events by dividing the country into 10 distinct regions and noting those counties struck most frequently with progressively darker shading.

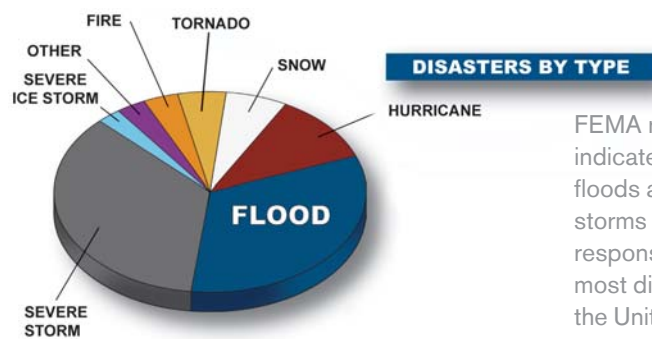


disposable tracheotomy kit is stocked in our inventory,” Dr. Rand said.

**GATHER YOUR FORCES.** Partnering with local organizations is an important asset that can make response efforts more effective. The success of a disaster plan can hinge on establishing relationships and coordinating team members from a variety of specialties. For example, the Houston Eye Care Emergency Disaster Response Plan is a collaboration between Prevent Blindness Texas, the Houston Ophthalmological Society and the University of Houston College of Optometry. It integrates the skills and assets from each of these entities, as well as local partnerships, into a cohesive response plan designed to serve the eye care needs of a population of more than 5,500,000 in 10 counties after a disaster. “It’s imperative to plan for various scenarios and have regional partnerships in case local capacity is overwhelmed. Prevent Blindness America is in the process of identifying all the fully equipped eye vans in the United States that could be called upon for regional response. These are valuable resources that are useful for providing onsite care in disasters that disrupt infrastructure,” said Dr. Coburn.

### 3. SAFETY AND SECURITY

“One of our main priorities is the safety of our staff and patients,” said Dr. Trattler. “It has to be the primary goal in the immediate short-term when a tropical storm or hurricane is looming offshore. We generally start canceling patients’ appointments about 36 hours before a hurricane is predicted to make landfall. While it is rare for our postoperative patients to experience complications, we advise them to continue their present medication and stay safe until the weather improves and we can schedule their follow-up



FEMA records indicate that floods and severe storms are responsible for most disasters in the United States.

appointment. We also close the office early enough so that those who will remain on duty in the hospital can prepare their homes and safely return.”

**ENSURE PHYSICAL SAFETY.** In an effort to reduce storm-related damage and keep the Rand Eye Institute operational during hurricanes, manual shutters were installed to protect the doors and windows from flying debris during a hurricane. The shutters are closed as soon as a watch is issued for the region, offering added protection for both patients and staff.

The aftermath of Hurricane Katrina brought physician responsibility for his or her patients to the fore. “The plan that we previously had in place at the University of Texas was to keep all of our patients in the hospital during a hurricane. It became evident after Hurricane Katrina that the plan had to be changed. Keeping 800 patients in the hospital without access to supplies for an extended period, along with the possibility of an interruption in utilities, is just not practical. Before we had a chance to practice the plan, Hurricane Rita was in the Gulf of Mexico. Thanks to thorough planning, however, everyone was successfully evacuated from the hospital within a couple of days,” recalled Dr. van Kuijk.

**CONTROL INFECTION OUTBREAKS.** A secondary consequence of a disaster is the rapid spread of



infectious disease. According to a 2007 article in the *American Journal of Infection Control*, “infection control issues in shelters, such as overcrowding, food-borne illness, lack of restroom facilities, inadequate environmental cleaning procedures and products, difficulty assessing disease outbreaks in shelters, an inability to isolate potentially contagious patients, and too few hand hygiene supplies can contribute to secondary disease transmission.”<sup>4</sup> Maintaining an adequate supply of gloves, masks and other protective wear as well as sterile hand washes and rubs for staff members is vital for keeping everyone safe.

**KEEP THOSE PREMIUMS PAID UP.** “You also have to plan for the safety of your practice,” said Dr. Trattler. “It is mandatory that everyone have business interruption insurance. Integral to the value of the insurance is keeping a backup copy of your patients’ names and phone numbers and your registration and financial information. It should be stored in a distant location that will be unharmed

by a local disaster. These items will be necessary to verify your assets should you need to file a claim, as well as restoring your practice.”

#### 4. STAFF RESPONSIBILITIES

All staff members should know their preassigned role in a disaster response, understand a clearly defined chain of command and have a set of checklists to guide their actions. Assigned roles can prevent redundancy of responsibilities as well as minimize confusion. Disaster drills and mock scenarios should be rehearsed to test both the plan and the staff for various contingencies. “There are three floors in our building: the clinic, the clinical offices and the research center. Each floor has a plan that outlines where supplies and diagnostic equipment should be moved during a disaster and who is in charge of moving it. The technical staff prepares the clinic. The secretaries prepare the offices on the second floor and the study monitor safeguards the study center. The plan designates who is essential for carrying out the plan and what their duties are so there is no confusion during an actual event,” said Dr. van Kuijk.

**GET READY TO TRIAGE.** “Training and preparation are essential to remain effective during major catastrophic events,” said Michael S. Baker, MD. In fact, for an article in *Military Medicine*, Dr. Baker writes, “Disaster triage and crisis management represent a tactical art that incorporates clinical skills, didactic information, communication ability, leadership and decision making. Planning, rehearsing and exercising various scenarios encourage the flexibility, adaptability and innovation required in disaster settings. These skills can

### PLAGUE, POISON OR PROTONS? MANAGING THE NEXT DISASTER

For all of their lethal power, hurricanes and earthquakes may be trumped by biologic, chemical and radiation disasters. *Yersinia pestis*, for example, the cause of bubonic plague and pneumonic plague, may have killed as many as 75 million people in Europe and Asia during what has been called the “calamitous” 14th century. That epidemic was followed by decades of monumental social and economic unrest. And some observers believe *Yersinia* could visit (or be visited upon us) again.

*Yersinia*, like *Brucella melitensis* or *Bacillus anthracis*, would hardly be described as a common presentation to most ophthalmologists. But the CDC is anticipating every possibility, including that of bioterrorists unleashing infectious agents on a

massive scale. Accordingly, the CDC maintains exhaustive Web pages designed to give health workers guidance for unprecedented situations.

Epidemics constitute just one of five primary disaster categories addressed by the CDC, all of which could demand the skills of ophthalmologists:

**Epidemic infections**, including anthrax, botulism, brucellosis (or undulant fever), cholera, plague (*Yersinia*), smallpox, tularemia, typhoid fever and the various hemorrhagic fevers.

**Chemical exposures** to biotoxins like brevetoxin and ricin, blistering agents such as nitrogen or sulfur mustard, blood agents like cyanide, caustics such as hydrofluoric acid, choking agents like chlorine and phosphorus, incapacitating agents like

bring order to the chaos of overwhelming disaster events.”<sup>5</sup> Dr. Baker is chairman of surgery at the John Muir Medical Center in Walnut Creek, Calif.

## 5. UTILITIES MANAGEMENT

Quite often, electrical power and potable water are unavailable after a disaster. Earthquakes can break gas and water lines, while hurricanes and tornadoes can down power lines and contaminate water by the introduction of fecal material and chemicals.

**DUMP DEAD BATTERIES.** “We review our inventory of emergency items such as flashlights, lanterns and batteries annually,” said Dr. Rand. “Our surgical pavilion has an emergency propane generator. To ensure that it functioning properly, we operate it on full-load monthly for 30 minutes, semiannually for two hours, and yearly for four hours to ensure it will work if we lose electric service. One contingency that we did not plan for two years ago, however, was determining how we were going to get propane delivered when the diesel trucks could not obtain any fuel. Our generator ran out of propane after five days, and we could only wait.”

## 6. PATIENT SURVIVAL AND SUPPORT

Last but, obviously, not least is the welfare of patients. The eye is particularly susceptible to injury during disasters and can be penetrated by flying debris, damaged by blunt impacts and traumatized by airborne smoke and toxins. From lacerations, foreign bodies and burns to orbital fractures and perforating injuries, eye injuries are common in many disasters. Management strategies, however, are improving. Referring to trauma

expertise gathered by U.S. military experience in Iraq, Dr. Coburn said, “It is providing valuable lessons in eye care under difficult circumstances, including triage and management of eye and multiple systemic injuries.”

**CARE FOR THE CAREGIVER.** It is often the rescue workers who suffer ocular injuries after a disaster. These may be sustained during the initial rescue efforts or during the cleanup afterward. Injuries can include irritation from smoke and airborne particulates, and lacerations and puncture wounds from falling or shifting debris.



## YOU CAN'T CHOOSE YOUR DISASTER

The type, time and target of a disaster are rarely possible to predict. “The primary objective of disaster planning and training is to ensure an adequate, competent and flexible response that will satisfy the acute needs resulting from any disaster while still meeting the baseline demands of the

aerosolized opioids, anticoagulants like warfarin, metallic poisons such as arsenic and thallium, nerve agents such as sarin and tabun, solvents like benzene, irritants like chloroacetophenone, toxic alcohols such as methanol or ethylene glycol, and nausea inducers like adamsite.

**Radiation emergencies**, including nuclear detonations, acute radiation syndrome, the effects of dirty bombs and contamination from radioactive isotopes (americium-241, cesium-137, cobalt-60, iodine-131, iridium-192, plutonium, polonium-210, strontium-90, uranium-235 and uranium-238).

**Mass casualties**, such as those from burns (chemical, electrical and explosive), blast trauma (tympanic membrane perforation, blast-wave pulmonary and abdominal injuries), projectile and

fragmentation injuries (including penetrating globe wounds), crush trauma (including reperfusion syndrome), and fractures and traumatic amputations.

**Natural disasters**, including well-known catastrophic earth, water and wind events.

For full details, visit [www.emergency.cdc.gov](http://www.emergency.cdc.gov). Be sure to click on the “more” option for the most detailed lists. The American Medical Association also maintains thoroughly detailed protocols for physicians facing large-scale emergencies (see “Disaster Resources”).

—Denny Smith



affected community,” said Dr. Coburn. “An experienced ophthalmology-led eye team with appropriate instruments and supplies is needed to effectively examine, triage and treat eye injuries during disasters.” Forewarned and forearmed, Eye M.D.s can help pull their patients and communities through the next big one.

- 1 Goolsby, C. A et al. Disaster Planning (2006). [www.emedicine.com/emerg/topic718.htm](http://www.emedicine.com/emerg/topic718.htm).
- 2 FEMA Federal Disaster Declarations (2007). [www.fema.gov/news/disasters.fema?year=2007](http://www.fema.gov/news/disasters.fema?year=2007).
- 3 FEMA Federal Disaster Declarations by year or state. [www.fema.gov/news/disaster\\_totals\\_annual.fema](http://www.fema.gov/news/disaster_totals_annual.fema).
- 4 Rebmann, T. et al. *Am J Infect Control* 2007;35(6):374–381.
- 5 Baker, M. S. et al. *Mil Med* 2007;172(3):232–236.

## DISASTER RESOURCES

**The National Trauma Data Bank** is designed to inform the medical community, the public and policy makers about issues that characterize the current state of emergency care. [www.facs.org/trauma/ntdb.html](http://www.facs.org/trauma/ntdb.html).

**The Wireless Information System for Emergency Responders** provides a range of information on hazardous substances, including substance identification support, physical characteristics, human health information, and containment and suppression advice. [www.wiser.nlm.nih.gov](http://www.wiser.nlm.nih.gov).

**The American Medical Association Management of Public Health Emergencies** (also available on a free CD-ROM) provides diagnostic and treatment protocols for a wide variety of crises. [www.ama-assn.org/ama/pub/category/18200.html](http://www.ama-assn.org/ama/pub/category/18200.html).

**The Department of Health and Human Services** provides information and resources to assist disaster responders. [www.hhs.gov/disasters/discussion/responders/index.html](http://www.hhs.gov/disasters/discussion/responders/index.html).

## MEET THE EXPERTS

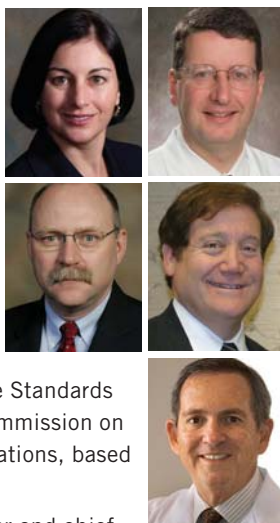
**AMY G. COBURN, MD** Associate professor of ophthalmology at Baylor College of Medicine in Houston.

**FREDERICUS VAN KUIJK, MD, PHD** Associate professor of ophthalmology, vice chairman of clinical services and medical director of vitreoretinal diseases at the University of Texas in Galveston.

**GEORGE MILLS** Senior engineer of the Standards Interpretation Group at the Joint Commission on Accreditation of Healthcare Organizations, based in Oakbrook Terrace, Ill.

**WILLIAM J. RAND, MD** Medical director and chief surgeon of the Rand Eye Institute, a private practice in Deerfield Beach, Fla.

**HENRY L. TRATTLER, MD** In private practice at the Center for Excellence in Eye Care in Miami.



BETIMOL® (timolol ophthalmic solution) 0.25%, 0.5%

### BRIEF SUMMARY

**INDICATIONS AND USAGE** Betimol® is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

**CONTRAINDICATIONS** Betimol® is contraindicated in patients with overt heart failure, cardiogenic shock, sinus bradycardia, second- or third-degree atrioventricular block, bronchial asthma or history of bronchial asthma, or severe chronic obstructive pulmonary disease, or hypersensitivity to any component of this product.

**WARNINGS** As with other topically applied ophthalmic drugs, Betimol® is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failure have been reported following systemic or topical administration of beta-adrenergic blocking agents. Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe cardiac failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Betimol® should be discontinued at the first sign or symptom of cardiac failure. Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma which are contraindications) should in general not receive beta-blocking agents. Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to a major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heart-beat has also been reported. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents is recommended. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of beta-adrenergic agonists. Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

**PRECAUTIONS** General Because of the potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Betimol®, alternative therapy should be considered. 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. (See PRECAUTIONS, Information for Patients.) Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalized weakness). Beta-adrenergic blocking agents have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms. In angle-closure glaucoma, the goal of the treatment is to reopen the angle. This requires constricting the pupil. Betimol® has no effect on the pupil. Therefore, if timolol is used in angle-closure glaucoma, it should always be combined with a miotic and not used alone. Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions. The preservative benzalkonium chloride may be absorbed by soft contact lenses. Patients who wear soft contact lenses should wait 5 minutes after instilling Betimol® before they insert their lenses. **Information for Patients** Patients should be instructed to avoid pulling the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions can 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. (See PRECAUTIONS, General.) Patients requiring concomitant topical ophthalmic medications should be instructed to administer these at least 5 minutes apart. Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, or cardiac failure should be advised not to take this product (See CONTRAINDICATIONS). **Drug Interactions** Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Betimol® should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. Patients should not usually receive two topical ophthalmic beta-adrenergic blocking agents concurrently. Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Calcium antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided. Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. **Injectable Epinephrine:** (See PRECAUTIONS, General, Anaphylaxis). **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity of timolol (as the maleate) has been studied in mice and rats. In a two-year study orally administered timolol maleate (300mg/kg/day) (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose) in male rats caused a significant increase in the incidence of adrenal pheochromocytomas; the lower doses, 25 mg or 100 mg/kg daily did not cause any changes. In a life span study in mice the overall incidence of neoplasms was significantly increased in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Furthermore, significant increases were observed in the incidences of benign and malignant pulmonary tumors, benign uterine polyps, as well as mammary adenocarcinomas. These changes were not seen at the daily dose level of 5 or 50 mg/kg (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). For comparison, the maximum recommended human oral dose of timolol maleate is 1 mg/kg/day. Mutagenic potential of timolol was evaluated *in vivo* in the micronucleus test and cytogenetic assay and *in vitro* in the neoplastic cell transformation assay and Ames test. In the bacterial mutagenicity test (Ames test) high concentrations of timolol maleate (5000 and 10,000 g/plate) statistically significantly increased the number of revertants in *Salmonella typhimurium* TA100, but not in the other three strains tested. However, no consistent dose-response was observed nor did the number of revertants reach the double of the control value, which is regarded as one of the criteria for a positive result in the Ames test. *In vivo* genotoxicity tests (the mouse micronucleus test and cytogenetic assay) and *in vitro* the neoplastic cell transformation assay were negative up to dose levels of 800 mg/kg and 100 g/mL, respectively. No adverse effects on male and female fertility were reported in rats at timolol oral doses of up to 150 mg/kg/day (21,000 times the systemic exposure following the maximum recommended human ophthalmic dose). **Pregnancy Teratogenic effects:** Category C: Teratogenicity of timolol (as the maleate) after oral administration was studied in mice and rabbits. No fetal malformations were reported in mice or rabbits at a daily oral dose of 50 mg/kg (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Betimol® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** Because of the potential for serious adverse reactions in nursing infants from timolol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric use:** Safety and efficacy in pediatric patients have not been established.

**ADVERSE REACTIONS** The most frequently reported ocular event in clinical trials was burning/stinging on instillation and was comparable between Betimol® and timolol maleate (approximately one in eight patients). The following adverse events were associated with use of Betimol® in frequencies of more than 5% in two controlled, double-masked clinical studies in which 184 patients received 0.25% or 0.5% Betimol®: **OCULAR:** Dry eyes, itching, foreign body sensation, discomfort in the eyes, eyelid erythema, conjunctival injection, and headache. **BODY AS A WHOLE:** Headache. The following side effects were reported in frequencies of 1 to 5%: **OCULAR:** Eye pain, epiphora, photophobia, blurred or abnormal vision, corneal fluorescein staining, keratitis, blepharitis and cataract. **BODY AS A WHOLE:** Allergic reaction, asthenia, common cold and pain in extremities. **CARDIOVASCULAR:** Hypertension. **DIGESTIVE:** Nausea. **METABOLIC/NUTRITIONAL:** Peripheral edema. **NERVOUS SYSTEM/PSYCHIATRY:** Dizziness and dry mouth. **RESPIRATORY:** Respiratory infection and sinusitis. In addition, the following adverse reactions have been reported with ophthalmic use of beta blockers: **OCULAR:** Conjunctivitis, blepharoptosis, decreased corneal sensitivity, visual disturbances including refractive changes, diplopia and retinal vascular disorder. **BODY AS A WHOLE:** Chest pain. **CARDIOVASCULAR:** Arrhythmia, palpitation, bradycardia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure and cardiac arrest. **DIGESTIVE:** Diarrhea. **ENDOCRINE:** Masked symptoms of hypoglycemia in insulin dependent diabetics (See WARNINGS). **NERVOUS SYSTEM/PSYCHIATRY:** Depression, impotence, increase in signs and symptoms of myasthenia gravis and paresthesia. **RESPIRATORY:** Dyspnea, bronchospasm, respiratory failure and nasal congestion. **SKIN:** Alopecia, hypersensitivity including localized and generalized rash, urticaria.

Rx Only

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