

NDA - 18 - 086

S - 052

NDA 18-086/S-052

Merck & Co., Inc.
Attention: William G. Roberts, M.D.
Director Regulatory Affairs
Sumneytown Pike
West Point, PA 19486

MAR 18 1998

Dear Dr. Roberts:

Please refer to your supplemental new drug application dated December 18, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TIMOPTIC® 0.25% and 0.5% (timolol maleate ophthalmic solution) Sterile Ophthalmic Solution.

We acknowledge receipt of your submission dated January 27, 1998.

The supplemental application provides for revisions to the Precautions and Adverse Reactions sections of the package insert.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 18, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

However, we have the following recommended revisions:

1. The generic name printed at the top of each column of the package insert should be revised so that it is in all lower case letters, as timolol maleate ophthalmic solution.
2. Under HYPERSENSITIVITY in the Adverse Events section, "systemic" should be inserted before "allergic reactions."
3. Under SPECIAL SENSES in the Adverse Events section, there should be a semicolon, rather than a comma, between "choroidal detachment following filtration surgery (see PRECAUTIONS, *General*)" and "tinnitus."
4. In the third paragraph of the Overdosage section, the dosage form, "tablets," should be added to the generic name of BLOCADREN.
5. The third paragraph of the Overdosage section is a sentence beginning "Significant lethality was observed..." This sentence may be deleted.

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Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 3/18/98

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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cc:

NDA 18-086

HFD-550/Div. files

HFD-550/Dep Dir/Chambers (with labeling)

HFD-550/MO/Ludwig (with labeling)

HFD-550/Clin Rev/Holmes (with labeling)

HFD-550/Proj Mgr/Gorski (with labeling)

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling)

HFI-20/Press Office (with labeling)

Drafted by: jh/March 2, 1998/18086s52.ap

Initialed by:

final:

APPROVAL (AP)

*jh 3/2/98
CC: 3/5/98*

Reviewed by: J. Holman 2/20/98

MAR 18 1997 **APPROVED**



9010840

TIMOPTIC® (Timolol Maleate Ophthalmic Solution)

MERCK & CO., INC.
West Point, PA 19486, USA

STERILE OPHTHALMIC SOLUTION

TIMOPTIC®

0.25% AND 0.5%

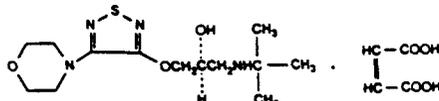
(TIMOLOL MALEATE
OPHTHALMIC SOLUTION)

DESCRIPTION

TIMOPTIC® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the *levo*-isomer. The nominal optical rotation of timolol maleate is:

$[\alpha]_{405}^{25}$ in 0.1N HCl (C = 5%) = -12.2°.

Its molecular formula is C₁₃H₂₄N₄O₃S·C₄H₄O₄ and its structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. TIMOPTIC is stable at room temperature.

TIMOPTIC Ophthalmic Solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths: Each mL of TIMOPTIC 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOPTIC 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action

Timolol maleate is a beta₁ and beta₂ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

TIMOPTIC Ophthalmic Solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of TIMOPTIC can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of TIMOPTIC is well maintained.

The precise mechanism of the ocular hypotensive action of TIMOPTIC is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Pharmacokinetics

In a study of plasma drug concentration in six subjects

greater reduction in intraocular pressure than 1, 2, 3, or 4 percent pilocarpine solution administered four times a day or 0.5, 1, or 2 percent epinephrine hydrochloride solution administered twice a day.

In these studies, TIMOPTIC was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. A slight reduction of resting heart rate in some patients receiving TIMOPTIC (mean reduction 2.9 beats/minute standard deviation 10.2) was observed.

INDICATIONS AND USAGE

TIMOPTIC Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

TIMOPTIC is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug 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 reactions 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 ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe 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. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

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, in which TIMOPTIC is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including TIMOPTIC.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to 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 experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of 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 that might precipitate a thyroid storm.

PRECAUTIONS

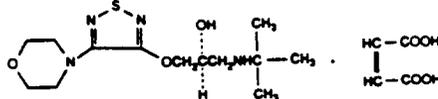
General

Because of potential effects of beta-adrenergic blocking agents on 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 TIMOPTIC, alternative therapy should be considered.

maleate possesses an optical activity of $+25^\circ$ and is provided as the levo-isomer. The nominal optical rotation of timolol maleate is:

$$[\alpha]_{405\text{ nm}}^{25^\circ} \text{ in } 0.1\text{N HCl (C = 5\%)} = -12.2^\circ.$$

Its molecular formula is $\text{C}_{13}\text{H}_{24}\text{N}_4\text{O}_3\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$ and its structural formula is:



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Pharmacokinetics

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily administration of TIMOPTIC 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

Clinical Studies

In controlled multiclinic studies in patients with untreated intraocular pressures of 22 mmHg or greater, TIMOPTIC 0.25 percent or 0.5 percent administered twice a day produced a

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PRECAUTIONS

General

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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.)

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol male-

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TIMOPTIC® (Timolol Maleate Ophthalmic Solution)

ate has little or no effect on the pupil. TIMOPTIC should not be used alone in the treatment of angle-closure glaucoma.

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.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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 should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

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.)

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

Drug Interactions

Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

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 result in vertigo, syncope, or postural hypotension.

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.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Injectable Epinephrine: (See PRECAUTIONS, *General, Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in

STERILE OPHTHALMIC SOLUTION
TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE OPHTHALMIC SOLUTION)

Circular Number 9010840



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The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been

(TIMOLOL MALEATE OPHTHALMIC SOLUTION)

Circular Number 9010840



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Original
NDA No: 18-036 Rev. 12-22-97
Reviewed by: J. Holmes 2/20/98

NDA 18-086

9010840
TIMOPTIC® (Timolol Maleate Ophthalmic Solution)

associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy-Teratogenic effects:

Pregnancy Category C. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. 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. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from TIMOPTIC in nursing infants, 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 effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE

Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR

Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE

Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC

Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC

Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN

Alopecia and psoriasisiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY

TIMOPTIC® (Timolol Maleate Ophthalmic Solution)

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: **Allergic:** Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; **Body as a Whole:** Extremity pain, decreased exercise tolerance, weight loss; **Cardiovascular:** Worsening of arterial insufficiency, vasodilatation; **Digestive:** Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; **Hematologic:** Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; **Endocrine:** Hyperglycemia, hypoglycemia; **Skin:** Pruritus, skin irritation, increased pigmentation, sweating; **Musculoskeletal:** Arthralgia; **Nervous System/Psychiatric:** Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; **Respiratory:** Rales, bronchial obstruction; **Urogenital:** Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTIC Ophthalmic Solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN® (timolol maleate). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

Significant lethality was observed in female rats and female mice after a single dose of 900 and 1190 mg/kg (5310 and 3570 mg/m²) of timolol, respectively.

An *in vitro* hemodialysis study, using ¹⁴C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

TIMOPTIC Ophthalmic Solution is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent TIMOPTIC in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day.

Since in some patients the pressure-lowering response to TIMOPTIC may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with TIMOPTIC.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents.)

HOW SUPPLIED

Sterile Ophthalmic Solution TIMOPTIC is a clear, colorless to light yellow solution.

No. 3366 — TIMOPTIC Ophthalmic Solution, 0.25% timolol equivalent, is supplied in a white, opaque, plastic OCUMETER® ophthalmic dispenser with a controlled drop tip as follows:

- NDC 0006-3366-32, 2.5 mL
- NDC 0006-3366-03, 5 mL
(6505-01-069-6518, 0.25% 5 mL)
- NDC 0006-3366-10, 10 mL
(6505-01-093-5458, 0.25% 10 mL)

highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy-Teratogenic effects:

Pregnancy Category C. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. 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. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from TIMOPTIC in nursing infants, 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 effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE

Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR

Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE

Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC

Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC

Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN

Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY

Signs and symptoms of allergic reactions, including angioedema, urticaria, and localized and generalized rash.

RESPIRATORY

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE

Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES

Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*), and tinnitus.

UROGENITAL

Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

cemia, hypoglycemia; *Skin*: Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal*: Arthralgia; *Nervous System/Psychiatric*: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory*: Rales, bronchial obstruction; *Urogenital*: Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdose with TIMOPTIC Ophthalmic Solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN® (timolol maleate). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

Significant lethality was observed in female rats and female mice after a single dose of 900 and 1190 mg/kg (5310 and 3570 mg/m²) of timolol, respectively.

An *in vitro* hemodialysis study, using ¹⁴C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

TIMOPTIC Ophthalmic Solution is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent TIMOPTIC in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day.

Since in some patients the pressure-lowering response to TIMOPTIC may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with TIMOPTIC.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

HOW SUPPLIED

Sterile Ophthalmic Solution TIMOPTIC is a clear, colorless to light yellow solution.

No. 3366 — TIMOPTIC Ophthalmic Solution, 0.25% timolol equivalent, is supplied in a white, opaque, plastic OCUMETER® ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3366-32, 2.5 mL
NDC 0006-3366-03, 5 mL
(6505-01-069-6518, 0.25% 5 mL)
NDC 0006-3366-10, 10 mL
(6505-01-093-5458, 0.25% 10 mL)
NDC 0006-3366-12, 15 mL

No. 3367 — TIMOPTIC Ophthalmic Solution, 0.5% timolol equivalent, is supplied in a white, opaque, plastic OCUMETER® ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3367-32, 2.5 mL
NDC 0006-3367-03, 5 mL
(6505-01-069-6519, 0.5% 5 mL)
NDC 0006-3367-10, 10 mL
(6505-01-092-0422, 0.5% 10 mL)
NDC 0006-3367-12, 15 mL

Storage

Store at room temperature, 15-30°C (59-86°F). Protect from freezing. Protect from light.

Dist. by:
 **MERCK & CO., INC.**, West Point, PA 19486, USA

Issued August 1997
Printed in USA

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STERILE OPHTHALMIC SOLUTION
TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE OPHTHALMIC SOLUTION)





■ ■

9010840



William G. Roberts, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

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January 27, 1998

Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products - HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



MERCK
Research Laboratories

ORIGINAL-

SNC-05

WGR
5/4/98

Dear Dr. Weintraub:

NDA 20-408: TRUSOPT® Ophthalmic Solution
NDA 18-086: TIMOPTIC® Ophthalmic Solution

Response to FDA Request

Reference is made to the NDAs cited above and to the January 14, 1998 telephone call from Ms. Joanne Holmes (FDA) to Dr. William Roberts (MRL) inquiring about the code numbers appearing in the HOW SUPPLIED Section of the U.S. Package Circular for TIMOPTIC® and TRUSOPT®.

The numbers that are not preceded by "NDC" are National Stock Numbers. These numbers are assigned by the government for the purpose of ordering product. These numbers are added to the labeling for each dosage strength/bottle size as the government assigns them; therefore, some dosage strengths/bottle sizes may not have yet been assigned a National Stock Number by the government.

These National Stock Numbers are not associated with American Hospital Formulary codes. Per request from FDA, Merck removed the American Hospital Formulary (A.H.F.S.) code from the TIMOPTIC® labeling in 1993 (Circular # 7115432) as well as from all of our other products by 1996. The U.S. Package Circular for TRUSOPT® never carried an A.H.F.S. code, as the product labeling was developed after Merck was notified of the FDA's preference for omission of this information.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

William G. Roberts, M.D.
Director, Regulatory Affairs

Certified No. P 963 205 853
Q/YAR/LAC/LTR/NDC

Desk Copy: Ms. Joanne Holmes, HFD-550, Certified No. 963 213 843

Clinical Review of NDA 18-086
Labeling Supplement

FEB 20 1998

NDA 18-086/S-052

Submission Dates: 12/18/97 & 1/27/98
Receipt Date: 12/22/97 & 1/30/98
Review Date: 2/20/98

Applicant: Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486

Applicant's Representative: William G. Roberts, M.D.
Director Regulatory Affairs
610-397-7052

Drug: Timoptic® (timolol maleate ophthalmic solution) Sterile
Ophthalmic Solution, 0.25% and 0.5%

Pharmacologic Category: Beta adrenergic blocker

Related Review: Medical Officer's Review #2 of NDA 20-869, Cosopt
(dorzolamide hydrochloride and timolol maleate ophthalmic
solution), dated 2/12/98.

Submitted: A Special Supplement-Changes Being Effected containing revised
labeling (as FPL) with additions and revisions to the Precautions
and Adverse Reactions sections. Other changes to the Clinical
Pharmacology, Precautions, Adverse Reactions, Dosage and
Administration, and How Supplied sections were previously made
and approved for S-047 and S-051, approved 5/16/97 and 8/5/97,
respectively, but FPL had not been sent in after the approval
letters. This submission of FPL includes those revisions.

Following is the labeling submitted by the company. Reviewer
recommended deletions are noted by ~~strikeout~~ and additions by
shading within the review.

9010840

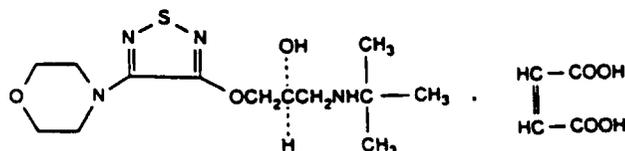
STERILE OPHTHALMIC SOLUTION
TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE
OPHTHALMIC SOLUTION)

DESCRIPTION

TIMOPTIC® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer. The nominal optical rotation of timolol maleate is:

$$[\alpha]_{405 \text{ nm}}^{25^\circ} \text{ in } 0.1\text{N HCl (C = 5\%)} = -12.2^\circ.$$

Its molecular formula is $\text{C}_{13}\text{H}_{24}\text{N}_4\text{O}_3\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$ and its structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. TIMOPTIC is stable at room temperature.

TIMOPTIC Ophthalmic Solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths: Each mL of TIMOPTIC 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOPTIC 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

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CLINICAL PHARMACOLOGY

Mechanism of Action

Timolol maleate is a beta₁ and beta₂ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

TIMOPTIC Ophthalmic Solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of TIMOPTIC can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of TIMOPTIC is well maintained.

The precise mechanism of the ocular hypotensive action of TIMOPTIC is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Pharmacokinetics

In a study of plasma drug concentration in six subjects, the systemic exposure of timolol was determined following twice daily administration of TIMOPTIC 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

Clinical Studies

In controlled multiclinic studies in patients with untreated intraocular pressures of 22 mmHg or greater, TIMOPTIC 0.25 percent or 0.5 percent administered twice a day produced a greater reduction in intraocular pressure than 1, 2, 3, or 4 percent pilocarpine solution administered four times a day or 0.5, 1, or 2 percent epinephrine hydrochloride solution administered twice a day.

In these studies, TIMOPTIC was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. A slight reduction of resting heart rate in some patients receiving TIMOPTIC (mean reduction 2.9 beats/minute standard deviation 10.2) was observed.

INDICATIONS AND USAGE

TIMOPTIC Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

TIMOPTIC is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug 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 reactions 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 ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe 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. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

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, in which TIMOPTIC is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including TIMOPTIC.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to 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 experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of 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 that might precipitate a thyroid storm.

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on 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 TIMOPTIC, 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*.)

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC should not be used alone in the treatment of angle-closure glaucoma.

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.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly, or if the tip of the dispensing container contacts the eye or surrounding structures, 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*.)

Reviewer's comments: *The following was added to the first sentence for consistency with other Merck ophthalmic labeling: "or if the tip of the dispensing container contacts the eye or surrounding structures."*
Acceptable.

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

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.)

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

Reviewer's comments: *The paragraph above was revised for consistency with other Merck ophthalmic labeling, from "The preservative in TIMOPTIC, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling TIMOPTIC before they insert their lenses." Acceptable.*

Drug Interactions

Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

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 result in vertigo, syncope, or postural hypotension.

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.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Reviewer's comments: *The precaution on quinidine has been added. Supporting literature and Worldwide Experience System (WAES) Reports were provided. Acceptable.*

Injectable Epinephrine: (See PRECAUTIONS, General, Anaphylaxis)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy-Teratogenic effects:

Pregnancy Category C. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations.

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. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from TIMOPTIC in nursing infants, 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 effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

Reviewer's comments:

Some adverse events previously listed under oral timolol have now been seen with timolol ophthalmic solution. They have been moved into the appropriate body systems in the paragraphs for timolol ophthalmic solution.

Adverse events newly reported for timolol ophthalmic solution, and not previously noted for oral timolol, have been added to the appropriate body system in the paragraph on oral timolol. The changes are acceptable.

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE

Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR

Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

Reviewer's comments: *Edema, claudication, Raynaud's phenomenon, and cold hands and feet were moved from the oral timolol paragraph.*

DIGESTIVE

Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC

Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC

Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

Reviewer's comments: *The above subsection was rearranged. Insomnia, nightmares, and memory loss were moved from the oral timolol paragraph.*

SKIN

Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY

Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash.

Reviewer's comments: *Alopecia and psoriasiform rash or exacerbation of psoriasis were added under Skin. Hypersensitivity is now a distinct paragraph, incorporating what had been under Skin, and adding angioedema.*

RESPIRATORY

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE

Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES

Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.

Reviewer's comments: *Dry eyes and tinnitus were moved from the oral timolol paragraph. The comma after "(see PRECAUTIONS, General)" should be replaced with a semicolon.*

UROGENITAL

Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

Reviewer's comments *Decreased libido and Peyronie's disease were moved from the oral timolol paragraph.*

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTIC Ophthalmic Solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ¹⁴C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

TIMOPTIC Ophthalmic Solution is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent TIMOPTIC in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day.

Since in some patients the pressure-lowering response to TIMOPTIC may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with TIMOPTIC.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

HOW SUPPLIED

Sterile Ophthalmic Solution TIMOPTIC is a clear, colorless to light yellow solution.

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No. 3366 — TIMOPTIC Ophthalmic Solution, 0.25% timolol equivalent, is supplied in a white, opaque, plastic OCUMETER* ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3366-32, 2.5 mL
NDC 0006-3366-03, 5 mL
(6505-01-069-6518, 0.25% 5 mL)
NDC 0006-3366-10, 10 mL
(6505-01-093-5458, 0.25% 10 mL)
NDC 0006-3366-12, 15 mL.

No. 3367 — TIMOPTIC Ophthalmic Solution, 0.5% timolol equivalent, is supplied in a white, opaque, plastic OCUMETER ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3367-32, 2.5 mL
NDC 0006-3367-03, 5 mL
(6505-01-069-6519, 0.5% 5 mL)
NDC 0006-3367-10, 10 mL
(6505-01-092-0422, 0.5% 10 mL)
NDC 0006-3367-12, 15 mL

Storage

Store at room temperature, 15-30°C (59-86°F). Protect from freezing. Protect from light.

Dist. by:

 **MERCK & CO., INC.**, West Point, PA 19486, USA

Issued August 1997

Printed in USA

Recommendations:

The changes proposed are acceptable, and an approval letter may be issued. Revisions noted in the review are recommendations that may be conveyed in the approval letter. They are not terms of approval. The revisions are as follows:

1. The generic name printed at the top of each column of the package insert should be revised so that it is in all lower case letters, as timolol maleate ophthalmic solution.

2. In the Adverse Events section, under HYPERSENSITIVITY, "systemic" should be inserted before "allergic reactions."
3. In the Adverse Events section, under SPECIAL SENSES, there should be a semicolon, rather than a comma, between "choroidal detachment following filtration surgery (see PRECAUTIONS, *General*)" and "tinnitus."
4. In the second paragraph of the Overdosage section, "tablets" should be added to the generic name of BLOCADREN to indicate the dosage form.
5. The third paragraph of the Overdosage section is a sentence beginning "Significant lethality was observed..." It may be deleted.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:

NDA 18-086

HFD-550/Div files

HFD-550/Dep Dir/Chambers

HFD-550/MO/Ludwig

HFD-550/Clin/Holmes

HFD-550/PM/Gorski

HF-2/MedWatch

WAC 3/16/98



Food and Drug Administration
Rockville MD 20857

NDA 18-086/S-052

Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004

DEC 29 1997

Attention: William G. Roberts, M.D.
Director, Regulatory Affairs

Dear Dr. Roberts:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: TIMOPTIC® (sterile ophthalmic solution)

NDA Number: 18-086

Supplement Number: S-052

Date of Supplement: December 18, 1997

Date of Receipt: December 22, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 20, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Chin Koerner 12/24/97
Chin Koerner, M.S.

Acting Supervisory Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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Page 2

cc:

Original NDA 18-086/S-052
HFD-550/Div. Files
HFD-550/CSO/Gorski, L.

SUPPLEMENT ACKNOWLEDGEMENT

William G. Roberts, M.D.
Director
Regulatory Affairs

NDA NO. 18086 REF. NO. SLR-052

NDA SUPPL FOR Labeling

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 7052

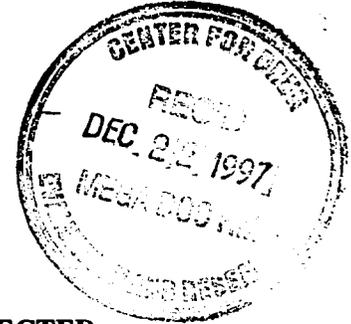
ORIGINAL

These copies are
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not desk copies.

December 18, 1997



Michael Weintraub, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products - HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850



Dear Dr. Weintraub:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 18-086: Sterile Ophthalmic Solution TIMOPTIC®
NDA 19-463: Preservative-Free Sterile Ophthalmic Solution TIMOPTIC® in OCUDOSE®
NDA 20-330: Sterile Ophthalmic Gel Forming Solution TIMOPTIC-XE®

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c) we submit a supplement to NDA 18-086.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 3 of the approved New Drug Application of Sterile Ophthalmic Solution TIMOPTIC®. The revisions to the label are described in the Summary of Revisions attached to the cover letter.

Attached as Changes Being Effectuated are the following:

1. Printed package circular #9010840 (Issued August 1997)
2. Annotated circular, illustrating the revisions
3. Supporting literature

The circular has been revised as outlined in the summary of revisions.

The revised labeling will be used in all packaging on or before 3/1/98 and in all product sold or distributed on or before 7/1/98.

A set of the revised bottle labels and cartons will be submitted after they are printed as needed for packaging.

A complete field copy of this supplement has been submitted to the FDA Philadelphia District Office.

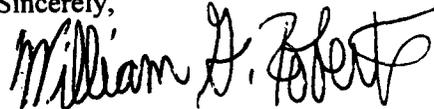
Michael Weintraub, M.D., Acting Director
NDA 18-086: TIMOPTIC®
NDA 19-463: TIMOPTIC® in OCUDOSE®
NDA 20-330: TIMOPTIC-XE®
Page 2

As required by Section 306(k)(1) of the Generic Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

We consider the filing of this supplement to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to William G. Roberts, M.D. (610/397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,



William G. Roberts, M.D.
Director
Regulatory Affairs

Attachments

Federal Express #1
Q/YAR/LAC/LTR/CBE-OPHT-1

Desk copy: Ms. Joanne Holmes, HFD-550, 9201 Corporate Blvd.
Federal Express #1

Desk Copy: Philadelphia District Office, FDA, U.S. Custom House
Room 900, 2nd & Chestnut Streets, Phila., PA 19106-2973
Federal Express # 2