NDA - 18 - 086

S - 047

APR 25 1997

Clinical Review of NDA 18-086
Labeling Supplement

NDA 18-086/S-047

Submission Dates: 12/2/96
3/7/97
3/25/97
Review Date: 4/5/97

Applicant: Merck & Co., Inc.
West Point, PA 19486

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

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

Pharmacologic Category: Beta adrenergic blocker

Submitted: Revised draft labeling in response to the August 7, 1996, approvable letter. The original supplement contained revisions in the Description, Clinical Pharmacology, Precautions, and Adverse Reactions sections of the package insert.

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

79504

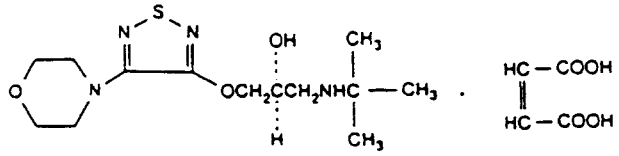
STERILE OPHTHALMIC SOLUTION
TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE
OPHTHALMIC SOLUTION)

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:

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

Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ 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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* Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

Timolol maleate is a $beta_1$ and $beta_2$ (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.

Reviewer's comments: *The applicant did not combine the last two sentences as provided in the revised draft labeling attached to the August 7, 1996, approvable letter. They retained the original proposed labeling. This is acceptable.*

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.

Reviewer's comments: *The rest of the above paragraph, as well as the paragraph that had followed, were deleted as requested.*

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.

Reviewer's comments: *The next 2 paragraphs that had followed were deleted as requested.*

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.

Reviewer's comments: *The next paragraph that had followed was deleted as requested.*

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.

Reviewer's comments: *The next paragraph that had followed was deleted as requested.*

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, 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.

Reviewer's comments: *The sentence above was revised as requested.*

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.)

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.

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.

Reviewer's comments: *The last sentence of the above paragraph was revised from "Patients should not usually receive two topical ophthalmic beta-adrenergic blocking agents concurrently." to "The concomitant use of two topical beta-adrenergic blocking agents is not recommended." This is acceptable.*

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.

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.

Reviewer's comments: *The dosage of oral timolol should be written as mg/kg/day for consistency.*

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, and pulmonary edema.

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

IMMUNOLOGIC
Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC
Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia, behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances.

SKIN
Hypersensitivity, including localized and generalized rash; urticaria, alopecia.

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, and itching and tearing; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; and choroidal detachment following filtration surgery (see PRECAUTIONS, *General*).

UROGENITAL
Retroperitoneal fibrosis and impotence.

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:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, 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, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties, Peyronie's disease.

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 ^{14}C 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.)

Reviewer's comments: *The applicant removed "with pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide" and added "other agents(s) for lowering intraocular pressure" after "concomitant therapy" in the second sentence of the above paragraph.*

The last two sentences were also added to the above paragraph: "The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, Drug Interactions, Beta-adrenergic blocking agents.)" This is acceptable.

The three paragraphs that followed were deleted as requested. This is acceptable.

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.

Reviewer's comments: *The word "controlled" was deleted from "controlled room temperature" as requested. This is acceptable.*

Dist. by:

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

Issued
Printed in USA

Recommendations: The majority of the revisions were made as requested. Additional revisions proposed by the applicant are acceptable. An approval letter may be issued, requesting the following revision:

In the first sentence of the second paragraph of the Carcinogenesis subsection of the Precautions section, the dose of oral timolol should be revised from 500 mg/kg to 500 mg/kg/day.

Joanne M. Holmes

Wiley A. Chambers, M.D.

cc:
NDA 18-086
HFD-550/Div files
HFD-550/Acting Div Dir/Chambers
HFD-550/MO/Ludwig ENE 4/25/97
HFD-550/Clin/Holmes
HFD-550//Proj Mgr/Gunter
HFD-550/Acting SPMS/LoBianco
HF-2/MedWatch

NDA 18-086/S-047

AUG - 7 1996

Merck Research Laboratories
William G. Roberts, M.D.
Director, Regulatory Affairs
Sumneytown Pike
West Point, PA 19486

Dear Dr. Roberts:

Please refer to your supplemental new drug application (NDA) dated October 12, 1995, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for TIMOPTIC® 0.25% and 0.5% (timolol maleate ophthalmic solution).

We also acknowledge your correspondence dated January 5, 1996.

The supplement provides for a draft labeling with revisions in the Description, Clinical Pharmacology, Precautions, and Adverse Reactions, special senses Sections of the package insert.

We have completed the review of this supplemental application as submitted with draft labeling and it is approvable. Before the supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL) identical to the attached revised version of the draft based on your January 5, 1996 submission.

Please submit sixteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact Mrs. Regina D. Joyce at 301-827-2015.

Sincerely yours,

AHC 5/6/96

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

cc:
NDA 18-086
HFD-550 DivFile
District Office
HFD-82
HFD-2/Lumpkin
HFD-40
HFD-550/SMO/Chambers
HFD-550/Chem/Tso
HFD-550/CSO/Holmes
HFD-550/Joyce 5/7/96

APPROVABLE (Supplement 047)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

12 pages

Clinical Review of NDA 18-086
Labeling Supplement

AUG - 7 1996

NDA NDA 18-086/S-047

Submission Dates: 10/12/95
1/5/96
Review Date: 2/9/96
Revised: 8/2/96

Applicant: Merck & Co.
West Point, PA 19486

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

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

Pharmacologic Category: Beta adrenergic blocker

Submitted: Final printed labeling with revisions in the Description, Clinical Pharmacology, Precautions, and Adverse Reactions sections of the package insert.

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

7950438

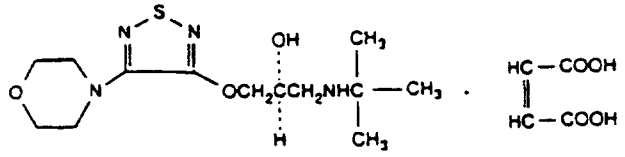
STERILE OPHTHALMIC SOLUTION
TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE
OPHTHALMIC SOLUTION)

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:

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

Its molecular formula is $C13H_{24}N4O3SC_4H4O_4$ 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.

Reviewer's Comments: *Molecular weight changed from 432.49 based on current IUPAC atomic weight for sulfur. Acceptable.*

® Registered trademark of MERCK & CO., Inc.

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

Timolol maleate is a beta$_1$ and beta$_2$ (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.

Reviewer's Comments: *The word "parasympathetic" has been corrected as requested. Acceptable.*

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-

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.

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.

Reviewer's Comments: *Editorial changes made for clarification. Acceptable.*

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).

Reviewer's Comments: *(e.g. timolol) has been put back in the insert as requested. Acceptable.*

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, 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.)

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.

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. Patients should not usually receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

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.

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, 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).

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, and pulmonary edema.

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

IMMUNOLOGIC
Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC
Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia, behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances.

SKIN
Hypersensitivity, including localized and generalized rash; urticaria, alopecia.

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, and itching and tearing; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; and choroidal detachment following filtration surgery (see PRECAUTIONS, *General*).

Reviewer's Comments: *"pseudopemphigoid" was added. The addition of this is presented in the form of adverse reactions that had been sent at various times to the NDA and resubmitted in this supplement for ease of review. It was originally submitted as "ocular pemphigoid" which is incorrect and revised to "pseudopemphigoid" in the amendment. Editorial changes were also made for clarification. Acceptable.*

UROGENITAL
Retroperitoneal fibrosis and impotence.

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:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, 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, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties, Peyronie's disease.

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 ^{14}C 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 pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted.

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 December 1995
Printed in USA

Recommendations: This labeling should be revised.

Regina D. Joyce

Wiley A. Chambers, M.D.

cc: NDA 18-086
HFD-550
HFD-550/MO/Chambers
HFD-550/CHEM/Tso
HFD-550/CSO/Holmes
HFD-550/CLIN/Joyce

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

Merck & Co., Inc.
P.O. Box 4, BLA-30
West Point PA 19486
Fax 610 397 2335
Tel 610 397 7052

October 12, 1995

ORIGINAL

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
HFD-540, Room 17B-45
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wilkin:

FINAL PRINTED LABELING
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 18-086: TIMOPTIC™ (Timolol Maleate Ophthalmic Solution)

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, the supplemental application provides for changes in Item 4(c)ii of the approved New Drug Application for TIMOPTIC™.

The circular has been revised as indicated in the Summary of Revisions. The cartons and labels were revised, for consistency, to add a storage statement.

Attached for submission are the following:

- 15 Copies of the Final Printed Package Circular (No. 7950437),
- Annotated package circular,
- Summary of Revisions,
- Supporting documentation for addition of Adverse Reaction (WAES Reports),
- 15 Copies each of cartons and labels -0.25% TIMOPTIC™ 2.5 mL, 5 mL, 10 mL, 15 mL,
- 15 Copies each of cartons and labels -0.5% TIMOPTIC™ 2.5mL, 5 mL, 10 mL, 15 mL.

Reference is made to your letter dated September 7, 1995 in which you request "(e.g. timolol)" be reinserted into the last sentence of the last paragraph in the General subsection of the PRECAUTIONS section. We will comply with your request by the first quarter of 1996.

The changes will become effective on or about September 1, 1995 and will apply to all packages of TIMOPTIC™ distributed from the company's manufacturing facilities at West Point, PA.

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

Questions concerning this supplemental application should be directed to William G. Roberts, M.D. (610/397-7052) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

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

Attachments

Certified No. P 914 179 335
Q/YARB/CARROLL/LTR/18086FPL

Holmes

NDA 18-086/S-047

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

MAY 16 1997

Dear Dr. Roberts:

Please refer to your October 12, 1995, supplemental new drug application 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 also refer to our approvable letter dated August 7, 1996.

We acknowledge receipt of your submissions dated December 2, 1996, and March 7 and 25, 1997.

This supplemental application provides draft labeling with revisions in the Description, Clinical Pharmacology, Precautions, and Adverse Reactions, Special Senses Sections of the package insert.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated March 25, 1997, with the revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The revision is as follows:

> Please revise the dose of oral timolol in the first sentence of the second paragraph of the Carcinogenesis subsection of the Precautions section, from 500 mg/kg to 500 mg/kg/day.

This revision is the term of the supplemental NDA approval.

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental application NDA 18-086/S-047. Approval of this FPL by FDA is not required before the labeling is used.

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

Please submit one market package of the drug 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.

This approval affects only the change specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

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

Sincerely,

WAC 5/16/97

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

cc:
NDA 18-086
HFD-550 Div Files
HF-2/MedWatch (with labeling)
HFD-40/DDMAC/Rumble (with labeling)
HFD-105/ODE V
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-550/MO/Ludwig (with labeling) EAS 4/23/97
HFD-550/Acting Div Dir/Chambers (with labeling)
HFD-550/Clin Rev/Holmes (with labeling) JH 4/4/97
HFD-550/Acting SPMS/LoBianco 4/28/97
HFD-550/Proj Mgr/Gunter (with labeling)

drafted: jh/March 3, 1997/18086s47.ap

APPROVAL