TABLETS

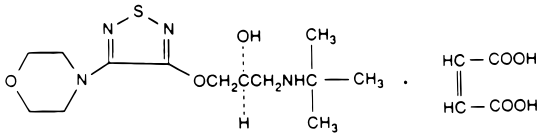
# TIMOLIDE®

## (TIMOLOL MALEATE-HYDROCHLOROTHIAZIDE)

### DESCRIPTION

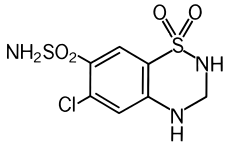
TIMOLIDE* (Timolol Maleate-Hydrochlorothiazide) is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a non-selective beta-adrenergic receptor blocking agent (timolol maleate) and a diuretic (hydrochlorothiazide).

Timolol maleate is (*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) salt. Its empirical formula is $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$ 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.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide has a molecular weight of 297.73. It is a white, or practically white, crystalline powder which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

TIMOLIDE is supplied as tablets containing 10 mg of timolol maleate and 25 mg of hydrochlorothiazide for oral administration. Inactive ingredients are cellulose, FD&C Blue 2, magnesium stearate, and starch.

### CLINICAL PHARMACOLOGY

*TIMOLIDE*

Timolol maleate and hydrochlorothiazide have been used singly and concomitantly for the treatment of hypertension. The antihypertensive effects of these agents are additive. The two components of TIMOLIDE have similar dosage schedules, and studies have shown that there is no interference with bioavailability when these agents are given together in the single combination tablet. Therefore, this combination provides a convenient formulation for the concomitant administration of these two entities.

In controlled clinical trials with TIMOLIDE in selected patients with mild to moderate essential hypertension, about 90 percent had a good to excellent response. In patients with more severe hypertension, TIMOLIDE may be administered with other antihypertensives such as ALDOMET* (Methyldopa) or a vasodilator.

Although the mechanisms of action of timolol maleate and hydrochlorothiazide in the treatment of hypertension have not been established, they are thought to be different; for example,

* Registered trademark of MERCK & CO., Inc.

hydrochlorothiazide increases plasma renin activity while timolol maleate reduces plasma renin activity.

*Timolol Maleate*

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 activity.

*Pharmacodynamics*

Clinical pharmacology studies have confirmed the beta-adrenergic blocking activity as shown by (1) changes in resting heart rate and response of heart rate to changes in posture; (2) inhibition of isoproterenol-induced tachycardia; (3) alteration of the response to the Valsalva maneuver and amyl nitrite administration; and (4) reduction of heart rate and blood pressure changes on exercise.

Timolol maleate decreases the positive chronotropic, positive inotropic, bronchodilator, and vasodilator responses caused by beta-adrenergic receptor agonists. The magnitude of this decreased response is proportional to the existing sympathetic tone and the concentration of timolol maleate at receptor sites.

In normal volunteers, the reduction in heart rate response to a standard exercise was dose dependent over the test range of 0.5 to 20 mg, with a peak reduction at 2 hours of approximately 30% at higher doses.

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.

Clinical studies indicate that timolol maleate at a dosage of 20-60 mg/day reduces blood pressure without causing postural hypotension in most patients with essential hypertension. Administration of timolol maleate to patients with hypertension results initially in a decrease in cardiac output, little immediate change in blood pressure, and an increase in calculated peripheral resistance. With continued administration of timolol maleate blood pressure decreases within a few days, cardiac output usually remains reduced, and peripheral resistance falls toward pretreatment levels. Plasma volume may decrease or remain unchanged during therapy with timolol maleate. In the majority of patients with hypertension, timolol maleate also decreases plasma renin activity. Dosage adjustment to achieve optimal antihypertensive effect may require a few weeks. When therapy with timolol maleate is discontinued, the blood pressure tends to return to pretreatment levels gradually. In most patients the antihypertensive activity of timolol maleate is maintained with long-term therapy and is well tolerated.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents is not established at this time. Possible mechanisms of action include reduction in cardiac output, reduction in plasma renin activity, and a central nervous system sympatholytic action.

*Pharmacokinetics and Metabolism*

Timolol maleate is rapidly and nearly completely absorbed (about 90%) following oral ingestion. Detectable plasma levels of timolol occur within one-half hour and peak plasma levels occur in about one to two hours. The drug half-life in plasma is approximately 4 hours and this is essentially unchanged in patients with moderate renal insufficiency. Timolol is partially metabolized by the liver and timolol and its metabolites are excreted by the kidney. Timolol is not extensively bound to plasma proteins; i.e., <10% by equilibrium dialysis and approximately 60% by ultrafiltration. 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. Plasma levels following oral administration are about half those following intravenous administration indicating approximately 50% first pass metabolism. The level of beta sympathetic activity varies widely among individuals, and no simple correlation exists between the dose or plasma level of timolol maleate and its therapeutic activity.

Therefore, objective clinical measurements such as reduction of heart rate and/or blood pressure should be used as guides in determining the optimal dosage for each patient.

*Hydrochlorothiazide*

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of thiazides may be related to the excretion and redistribution of body sodium. Hydrochlorothiazide usually does not cause clinically important changes in normal blood pressure.

## INDICATIONS AND USAGE

TIMOLIDE is indicated for the treatment of hypertension.

**This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to an individual patient's needs, it may be more convenient than the separate components.**

## CONTRAINDICATIONS

TIMOLIDE is contraindicated in patients with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; anuria; hypersensitivity to this product or to sulfonamide-derived drugs.

## WARNINGS

*Cardiac Failure*

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with TIMOLIDE should be withdrawn.

*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, patients receiving TIMOLIDE should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, TIMOLIDE should be withdrawn.

*Renal and Hepatic Disease and Electrolyte Disturbances*

Since timolol maleate is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Although the pharmacokinetics of timolol maleate are not greatly altered by renal impairment, marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20 mg doses. Dosing in such patients should therefore be especially cautious.

In patients with renal disease, thiazides may precipitate azotemia, and cumulative effects may develop in the presence of impaired renal function. If progressive renal impairment becomes evident, TIMOLIDE should be discontinued.

In patients with impaired hepatic function or progressive liver disease, even minor alterations in fluid and electrolyte balance may precipitate hepatic coma. Hepatic encephalopathy, manifested by tremors, confusion, and coma, has been reported in association with diuretic therapy including hydrochlorothiazide.

*Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal* — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of

such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

*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 'TIMOLIDE' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOLIDE'. However, if TIMOLIDE is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

*Major Surgery*

The necessity or desirability of withdrawal of beta-blocking therapy 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 been subject to 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 such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE).

*Metabolic and Endocrine Effects*

Beta-adrenergic blockade 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 blockade which might precipitate a thyroid storm. Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. Therefore, TIMOLIDE should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Insulin requirements in diabetic patients may be increased, decreased, or unchanged by thiazides. Diabetes mellitus which has been latent may become manifest during administration of thiazide diuretics.

Because calcium excretion is decreased by thiazides, TIMOLIDE should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

## PRECAUTIONS

*General*

*Electrolyte and Fluid Balance Status:* Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance, i.e., hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Thiazides have been shown to increase urinary excretion of magnesium, which may result in hypomagnesemia.

*Effects on Cholesterol and Triglyceride Levels:* Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

*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.

*Cerebrovascular Insufficiency:* Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow are observed, consideration should be given to discontinuing these agents.

*Drug Interactions*

TIMOLIDE may potentiate the action of other antihypertensive agents used concomitantly. Close observation of the patient is recommended when TIMOLIDE is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs has been reported. In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when TIMOLIDE and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired therapeutic effect has been obtained.

Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, e.g. nifedipine, while left ventricular failure and AV conduction disturbances were more likely to occur with either verapamil or diltiazem.

Intravenous calcium antagonists should be used with caution in patients receiving beta-adrenergic blocking agents.

The concomitant use of beta-adrenergic blocking agents with digitalis and either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

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.

Beta adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

*Risk from Anaphylactic Reaction:* While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction 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.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with TIMOLIDE.

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

Carcinogenicity, mutagenicity, and fertility studies have not been conducted in animals with TIMOLIDE.

*Timolol maleate:* In a two-year study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (250 times** the maximum recommended daily human dose). Similar differences were not observed in rats administered doses equivalent to approximately 20 or 80 times** the maximum recommended daily human dose.

In a lifetime study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day, (approximately 400 times** the maximum recommended daily human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin that occurred in female mice administered 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 which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended daily human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated *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

** Based on patient weight of 50 kg

employed, 5000 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 three additional strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 125 times** the maximum recommended daily human dose.

*Hydrochlorothiazide:* Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* in strains TA98, TA100, TA1535, TA1537, and TA1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

*Pregnancy*

*Teratogenic Effects - Pregnancy Category C.* Combinations of timolol maleate and hydrochlorothiazide were studied for teratogenic potential in the mouse and rabbit. The timolol maleate/hydrochlorothiazide combinations were administered orally to pregnant mice and pregnant rabbits at dosage levels of 1/2.5, 4/10, or 8/10 mg/kg/day. No teratogenic, embryotoxic, fetotoxic, or maternotoxic effects attributable to treatment were observed in either species. There are no adequate and well-controlled studies in pregnant women with TIMOLIDE. Because of the data listed below with the individual components, TIMOLIDE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Timolol Maleate:* Teratogenicity studies with timolol maleate in mice, rats and rabbits at doses up to 50 mg/kg/day (approximately 40 times** the maximum recommended daily human dose) showed 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 (approximately 830 times** the maximum recommended daily human 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 approximately 40 times** the maximum recommended daily human dose, in this case without apparent maternotoxicity.

*Hydrochlorothiazide:* Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

*Nonteratogenic Effects.*

*Hydrochlorothiazide:* TIMOLIDE contains hydrochlorothiazide. Thiazides cross the placental barrier and appear in cord blood. The possible hazards to the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

*Nursing Mothers*

Timolol maleate and thiazides have been detected in human milk. Because of the potential for serious adverse reactions from timolol and hydrochlorothiazide 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.

*Geriatric Use*

Clinical studies of TIMOLIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See WARNINGS, *Renal and Hepatic Disease and Electrolyte Disturbances.*)

## ADVERSE REACTIONS

TIMOLIDE is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient.

The adverse reactions listed in the following table were spontaneously reported and have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence was obtained from clinical studies conducted in the United States (257 patients treated with TIMOLIDE).

| Incidence Greater Than 1% | Incidence Less Than 1% |
|---|---|
| BODY AS A WHOLE | |
| fatigue/tiredness (1.9%) | chest pain |
| asthenia (1.9%) | headache |
| CARDIOVASCULAR | |
| hypotension (1.6%) | arrhythmia |
| bradycardia (1.2%) | syncope |
| | cardiac failure |
| DIGESTIVE SYSTEM | |
| none | diarrhea |
| | dyspepsia |
| | nausea |
| | gastrointestinal pain |
| | constipation |
| INTEGUMENTARY | |
| none | rash |
| | increased pigmentation |
| | dry mucous membranes |
| MUSCULOSKELETAL | |
| none | myalgia |
| NERVOUS SYSTEM | |
| dizziness (1.2%) | none |
| PSYCHIATRIC | |
| none | insomnia |
| | decreased libido |
| | nervousness |
| | confusion |
| | trouble concentrating |
| | somnolence |
| RESPIRATORY | |
| bronchial spasm (1.6%) | rales |
| dyspnea (1.2%) | |
| UROGENITAL | |
| none | renal colic |

The following additional adverse effects have been reported in clinical experience with the drug: cerebral ischemia, cerebral vascular accident, gout, muscle cramps, oculogyric crisis, worsening of chronic obstructive pulmonary disease, earache, and impotence.

*Other adverse reactions* that have been reported with the individual components are listed below:

*Timolol Maleate — Body as a Whole:* extremity pain, decreased exercise tolerance, weight loss, fever; *Cardiovascular:* cardiac arrest, cerebral vascular accident, worsening of angina pectoris, sinoatrial block, AV block, worsening of arterial insufficiency, Raynaud's phenomenon, claudication, palpitations, vasodilatation, cold hands and feet, edema; *Digestive:* hepatomegaly, elevated liver function tests, vomiting; *Hematologic:* nonthrombocytopenic purpura; *Endocrine:* hyperglycemia, hypoglycemia; *Skin:* skin irritation, pruritus, sweating, alopecia; *Musculoskeletal:* arthralgia; *Nervous System:* local weakness, vertigo, paresthesia, increase in signs and symptoms of myasthenia gravis; *Psychiatric:* depression, nightmares, hallucinations; *Respiratory:* cough; *Special Senses:* visual disturbances, diplopia, ptosis, eye irritation, dry eyes, tinnitus; *Urogenital:* urination difficulties.

There have been reports of retroperitoneal fibrosis in patients receiving timolol maleate and in patients receiving other beta-adrenergic blocking agents. A causal relationship between this condition and therapy with beta-adrenergic blocking agents has not been established.

*Hydrochlorothiazide — Body as a Whole:* weakness; *Digestive:* anorexia, gastric irritation, vomiting, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis; *Nervous System/Psychiatric:* vertigo, paresthesias, restlessness; *Hematologic:* leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; *Cardiovascular:*

hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs); *Hypersensitivity:* purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Metabolic:* hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance (see PRECAUTIONS); *Musculoskeletal:* muscle spasm; *Renal:* renal failure, renal dysfunction, interstitial nephritis, (see WARNINGS); *Skin:* erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* transient blurred vision, xanthopsia.

*Potential Adverse Effects:* In addition, a variety of adverse effects not observed in clinical trials with timolol maleate, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of timolol maleate: *Nervous System:* 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 performances on neuropsychometrics; *Cardiovascular:* intensification of AV block (see CONTRAINDICATIONS); *Digestive:* mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* agranulocytosis, thrombocytopenic purpura; *Allergic:* erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Miscellaneous:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TIMOLIDE or BLOCADREN* (timolol maleate).

*Clinical Laboratory Test Findings:* Clinically important changes in standard laboratory parameters were rarely associated with the administration of TIMOLIDE. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in serum triglycerides and uric acid and decreases in serum potassium and chloride. Decreases in HDL cholesterol have been reported.

## OVERDOSAGE

No data are available with regard to overdosage with TIMOLIDE in humans.

Pretreatment of mice with hydrochlorothiazide (5 mg/kg) did not alter the $LD_{50}$ of timolol (1320 mg/kg compared to 1300 mg/kg without pretreatment).

No specific information is available on the treatment of overdosage with TIMOLIDE, and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with TIMOLIDE should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance, and hypotension by established procedures.

*Timolol Maleate*

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate). A 30-year-old female ingested 650 mg of BLOCADREN (maximum recommended daily dose — 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.

The oral $LD_{50}$ of the drug is 1190 and 900 mg/kg in female mice and female rats, 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.

The most common signs and symptoms to be expected with overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. If overdosage occurs the following therapeutic measures should be considered:

(1) *Gastric lavage.*

(2) *Symptomatic bradycardia:* Use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

(3) *Hypotension:* Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

(4) *Bronchospasm:* Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

(5) *Acute cardiac failure:* Conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which has been reported to be useful.

(6) *Heart block (second or third degree):* Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

*Hydrochlorothiazide*

The most common signs and symptoms observed with hydrochlorothiazide overdosage are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

## DOSAGE AND ADMINISTRATION

The recommended starting and maintenance dosage is 1 tablet twice a day or 2 tablets once a day. Hydrochlorothiazide can be given at doses of 12.5 to 50 mg per day when used alone. If the antihypertensive response is not satisfactory, another nondiuretic antihypertensive agent may be added.

## HOW SUPPLIED

No. 3373 — Tablets TIMOLIDE 10-25 are light blue, flat, hexagonal-shaped, compressed tablets, with code MSD 67 on one side and TIMOLIDE on the other. Each tablet contains 10 mg of timolol maleate and 25 mg of hydrochlorothiazide. They are supplied as follows:

**NDC** 0006-0067-68 bottles of 100.

*Storage*

Store at controlled room temperature, 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

---

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued May 2002
Printed in USA