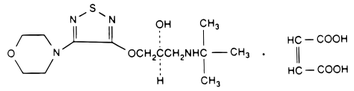
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

TABLETS
BLOCADREN®
(TIMOLOL MALEATE)

DESCRIPTION

BLOCADREN* (Timolol Maleate) is a non-selective beta-adrenergic receptor blocking agent. The chemical name for 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. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. Its empirical 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.

BLOCADREN is supplied as tablets in three strengths containing 5 mg, 10 mg or 20 mg timolol maleate for oral administration. Inactive ingredients are cellulose, FD&C Blue 2, magnesium stearate, and starch.

CLINICAL PHARMACOLOGY

BLOCADREN 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.

BLOCADREN 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 BLOCADREN 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 BLOCADREN at a dosage of 20-60 mg/day reduces blood pressure without causing postural hypotension in most patients with essential hypertension. Administration of BLOCADREN 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 BLOCADREN, 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 BLOCADREN. In the majority of patients with hypertension BLOCADREN also decreases plasma renin activity. Dosage adjustment to achieve optimal antihypertensive effect may require a few weeks. When therapy with BLOCADREN is discontinued, the blood pressure tends to return to pretreatment levels gradually. In most patients the antihypertensive activity of BLOCADREN 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.

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A Norwegian multi-center, double-blind study, which included patients 20 to 75 years of age, compared the effects of timolol maleate with placebo in 1,884 patients who had survived the acute phase of a myocardial infarction. Patients with systolic blood pressure below 100 mm Hg, sick sinus syndrome and contraindications to beta blockers, including uncontrolled heart failure, second or third degree AV block and bradycardia (<50 beats per minute), were excluded from the multi-center trial. Therapy with BLOCADREN, begun 7 to 28 days following infarction, was shown to reduce overall mortality; this was primarily attributable to a reduction in cardiovascular mortality. BLOCADREN significantly reduced the incidence of sudden deaths (deaths occurring without symptoms or within 24 hours of the onset of symptoms), including those occurring within one hour, and particularly instantaneous deaths (those occurring without preceding symptoms). The protective effect of BLOCADREN was consistent regardless of age, sex or site of infarction. The effect was clearest in patients with a first infarction who were considered at a high risk of dying, defined as those with one or more of the following characteristics during the acute phase: transient left ventricular failure, cardiomegaly, newly appearing atrial fibrillation or flutter, systolic hypotension, or SGOT (ASAT) levels greater than four times the upper limit of normal. Therapy with BLOCADREN also reduced the incidence of non-fatal reinfarction. The mechanism of the protective effect of BLOCADREN is unknown.

BLOCADREN was studied for the prophylactic treatment of migraine headache in placebo-controlled clinical trials involving 400 patients, mostly women between the ages of 18 and 66 years. Common migraine was the most frequent diagnosis. All patients had at least two headaches per month at baseline. Approximately 50 percent of patients who received BLOCADREN had a reduction in the frequency of migraine headache of at least 50 percent, compared to a similar decrease in frequency in 30 percent of patients receiving placebo. The most common cardiovascular adverse effect was bradycardia (5%).

Pharmacokinetics and Metabolism

BLOCADREN 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.

INDICATIONS AND USAGE

Hypertension

BLOCADREN is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Myocardial Infarction

BLOCADREN is indicated in patients who have survived the acute phase of myocardial infarction, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction.

Migraine

BLOCADREN is indicated for the prophylaxis of migraine headache.

CONTRAINDICATIONS

BLOCADREN 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; hypersensitivity to this product.

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 BLOCADREN 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 BLOCADREN should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, BLOCADREN should be withdrawn.

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 'BLOCADREN' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'BLOCADREN'. However, if BLOCADREN 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).

Diabetes Mellitus

BLOCADREN 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 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.

PRECAUTIONS

General

Impaired Hepatic or Renal Function: Since BLOCADREN 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.

Dosing in the Presence of Marked Renal Failure: Although the pharmacokinetics of BLOCADREN 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.

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.

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Drug Interactions

Catecholamine-depleting drugs: Close observation of the patient is recommended when BLOCADREN 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.

Non-steroidal anti-inflammatory drugs: Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs has been reported. When using these agents concomitantly, patients should be observed carefully to confirm that the desired therapeutic effect has been obtained.

Calcium antagonists: 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.

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

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

Clonidine: 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 human dose). Similar differences were not observed in rats administered doses equivalent to approximately 20 or 80 times** the maximum recommended 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 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 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 human dose.

** Based on patient weight of 50 kg

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Pregnancy

Pregnancy Category C. Teratogenicity studies with timolol 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. There are no adequate and well-controlled studies in pregnant women. BLOCADREN 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.

Because of the potential for serious adverse reactions from timolol 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 BLOCADREN for the treatment of hypertension or migraine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In a clinical study of BLOCADREN in patients who had survived the acute phase of a myocardial infarction, approximately 350 patients (37%) were 65-75 years of age. Safety and efficacy were not different between these patients and younger patients (see CLINICAL PHARMACOLOGY, *Pharmacodynamics*).

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 PRECAUTIONS, *Impaired Hepatic or Renal Function* and *Dosing in the Presence of Marked Renal Failure*.)

ADVERSE REACTIONS

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

In a multicenter (12-week) clinical trial comparing timolol maleate and placebo in hypertensive patients, the following adverse reactions were reported spontaneously and considered to be causally related to timolol maleate:

	Timolol Maleate (n = 176) %	Placebo (n = 168) %
BODY AS A WHOLE		
fatigue/tiredness	3.4	0.6
headache	1.7	1.8
chest pain	0.6	0
asthenia	0.6	0
CARDIOVASCULAR		
bradycardia	9.1	0
arrhythmia	1.1	0.6
syncope	0.6	0
edema	0.6	1.2
DIGESTIVE		
dyspepsia	0.6	0.6
nausea	0.6	0
SKIN		
pruritus	1.1	0
NERVOUS SYSTEM		
dizziness	2.3	1.2
vertigo	0.6	0
paresthesia	0.6	0
PSYCHIATRIC		
decreased libido	0.6	0
RESPIRATORY		
dyspnea	1.7	0.6
bronchial spasm	0.6	0
rales	0.6	0
SPECIAL SENSES		
eye irritation	1.1	0.6
tinnitus	0.6	0

These data are representative of the incidence of adverse effects that may be observed in properly selected patients treated with BLOCADREN, i.e., excluding patients with bronchospastic disease, congestive heart failure or other contraindications to beta blocker therapy.

In patients with migraine the incidence of bradycardia was 5 percent.

In a coronary artery disease population studied in the Norwegian multi-center trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups were:

	Adverse Reaction***		Withdrawal†	
	Timolol (n=945) %	Placebo (n=939) %	Timolol (n=945) %	Placebo (n=939) %
Asthenia or Fatigue	5	1	<1	<1
Heart Rate <40 beats/minute	5	<1	4	<1
Cardiac Failure-Nonfatal	8	7	3	2
Hypotension	3	2	3	1
Pulmonary Edema-Nonfatal	2	<1	<1	<1
Claudication	3	3	1	<1
AV Block - 2nd or 3rd degree	<1	<1	<1	<1
Sinoatrial Block	<1	<1	<1	<1
Cold Hands and Feet	8	<1	<1	0
Nausea or Digestive Disorders	8	6	1	<1
Dizziness	6	4	1	0
Bronchial Obstruction	2	<1	1	<1

***When an adverse reaction recurred in a patient, it is listed only once.

†Only principal reason for withdrawal in each patient is listed. These adverse reactions can also occur in patients treated for hypertension.

The following additional adverse effects have been reported in clinical experience with the drug: *Body as a Whole:* anaphylaxis, extremity pain, decreased exercise tolerance, weight loss, fever; *Cardiovascular:* cardiac arrest, cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation; *Digestive:* gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia; *Hematologic:* nonthrombocytopenic purpura; *Endocrine:* hyperglycemia, hypoglycemia; *Skin:* rash, skin irritation, increased pigmentation, sweating, alopecia; *Musculoskeletal:* arthralgia; *Nervous System:* local weakness, increase in signs and symptoms of myasthenia gravis; *Psychiatric:* depression, nightmares, somnolence, insomnia, nervousness, diminished concentration, hallucinations; *Respiratory:* cough; *Special Senses:* visual disturbances, diplopia, ptosis, dry eyes; *Urogenital:* impotence, 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.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with BLOCADREN, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of BLOCADREN: *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 performance 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 BLOCADREN.

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of BLOCADREN. Slight increases in blood urea nitrogen, serum potassium, uric acid, and triglycerides, and slight decreases in hemoglobin, hematocrit and HDL cholesterol occurred, but were not progressive or associated with clinical manifestations. Increases in liver function tests have been reported.

OVERDOSAGE

Overdosage has been reported with Tablets BLOCADREN. 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. Therapy with BLOCADREN should be discontinued and the patient observed closely. The following additional 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.

DOSAGE AND ADMINISTRATION

Hypertension

The usual initial dosage of BLOCADREN is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20-40 mg per day. Increases in dosage to a maximum of 60 mg per day divided into two doses may be necessary. There should be an interval of at least seven days between increases in dosages.

BLOCADREN may be used with a thiazide diuretic or with other antihypertensive agents. Patients should be observed carefully during initiation of such concomitant therapy.

Myocardial Infarction

The recommended dosage for long-term prophylactic use in patients who have survived the acute phase of a myocardial infarction is 10 mg given twice daily (see CLINICAL PHARMACOLOGY).

Migraine

The usual initial dosage of BLOCADREN is 10 mg twice a day. During maintenance therapy the 20 mg daily dosage may be administered as a single dose. Total daily dosage may be increased to a maximum of 30 mg, given in divided doses, or decreased to 10 mg once per day, depending on clinical response and tolerability. If a satisfactory response is not obtained after 6-8 weeks use of the maximum daily dosage, therapy with BLOCADREN should be discontinued.

HOW SUPPLIED

No. 3343 — Tablets BLOCADREN, 5 mg, are light blue, round, compressed tablets, with code MSD 59 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0059-68 bottles of 100.

No. 3344 — Tablets BLOCADREN, 10 mg, are light blue, round, scored, compressed tablets, with code MSD 136 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0136-68 bottles of 100

No. 3371 — Tablets BLOCADREN, 20 mg, are light blue, capsule shaped, scored, compressed tablets, with code MSD 437 on one side and BLOCADREN on the other. They are supplied as follows:

NDC 0006-0437-68 bottles of 100

Storage

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

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