INJECTION/TABLETS

BLOCADREN®

(timolol maleate, MSD)

BLOCADREN® (timolol maleate, MSD) is a beta-adrenergic receptor blocking agent. **BLOCADREN** is used for the treatment of essential hypertension (including the hyperkinetic heart syndrome) and for angina pectoris due to ischemic heart disease.

BLOCADREN reduces blood pressure without acute hypotensive episodes in most patients with essential hypertension. **BLOCADREN** usually does not affect normal blood pressure.

BLOCADREN effectively delays or prevents the development of anginal pain in most patients. It acts by modifying the cardiac response to stress or exercise.

BLOCADREN has been shown to be highly effective in reducing the incidence of cardiac death, including sudden death, and of reinfarction in patients who have survived the acute phase of a myocardial infarction.

BLOCADREN is also indicated in the prophylactic treatment of patients with common and classic migraine in which it effectively reduces the incidence of attacks, as well as in the treatment of supraventricular arrhythmia: paroxysmal atrial tachycardia, and atrial fibrillation.

INDICATIONS

BLOCADREN is indicated in:

- Essential hypertension (including the hyperkinetic heart syndrome)
- Angina pectoris due to ischemic heart disease
- Ischemic heart disease to reduce infarct size in patients in the early phase of acute myocardial infarction. Therapy is initiated with intravenous **BLOCADREN** and followed with tablets
- Ischemic heart disease to reduce the risk of cardiac death, including sudden death, and reinfarction in those who have survived the acute phase of myocardial infarction
- Supraventricular arrhythmias: paroxysmal atrial tachycardia, atrial fibrillation. Therapy is initiated with intravenous **BLOCADREN** and followed with tablets
- The prophylactic treatment of common and classic migraine.

DOSAGE AND ADMINISTRATION

Hypertension

The initial dosage is 10 mg a day given orally in a single or divided dose. Depending on the response of the patient, increases in dosage can be made to a maximum of 60 mg daily. Daily dosages above 20 mg should be given on a divided dose schedule.

Studies have shown that when **BLOCADREN** is administered concomitantly with **MODURETIC** (50 mg hydrochlorothiazide and 5 mg amiloride HCl) the majority of patients will respond to a regimen of 10 or 20 mg of **BLOCADREN** given orally once daily and one tablet of **MODURETIC**.

BLOCADREN may also be used with thiazides, hydralazine, or methyldopa. Dosage adjustments are usually required.

For concomitant use with catecholamine-depleting drugs such as reserpine or guanethidine, see **PRECAUTIONS**.

Angina

Therapy should be initiated with 5 mg orally two or three times a day. Depending on the symptomatic response, pulse rate, and blood pressure, increases in dosage may be necessary. The first increase should not exceed 10 mg per day in divided doses. Subsequent increases should not exceed 15 mg per day in divided doses. There should be an interval of at least three days between increases in dosage.

The usual dosage range of **BLOCADREN** is 15 mg to 45 mg per day. The majority of patients respond to a daily dosage of 35 mg to 45 mg.

Reduction of Infarct size

The recommended initial dose is 1 mg intravenously followed 10 minutes later by another intravenous dose of 1 mg. Whenever possible, therapy should be initiated within the first six hours of the onset of pain, and continued for 24 hours with an intravenous infusion at the rate of 0.6 mg/hr. After the first 24 hours treatment may be continued with tablets **BLOCADREN** at a dose of 10 mg twice a day.

Prophylactic use in ischemic heart disease

The usual dosage for long-term prophylactic use in patients who have survived the acute phase of a myocardial infarction is 10 mg orally given twice daily.

Paroxysmal atrial tachycardia and atrial fibrillation

The recommended initial dose is 1 mg intravenously followed, if necessary, by a second and a third dose of 1 mg intravenously each at 20 minutes intervals. Treatment may be continued with tablets **BLOCADREN** at a dose of 10 mg twice a day, the initial dose to be administered 1 hour after the last intravenous dose.

In patients with atrial fibrillation or flutter, treatment may be initiated with Tablets **BLOCADREN** at a starting dose of 10 mg twice a day which may be adjusted upward to 30 mg twice a day, based on clinical response.

Migraine

The recommended dosage in the prophylactic treatment of common and classic migraine is 10 mg to 20 mg administered orally once a day.

CONTRAINDICATIONS

- Bronchospasm (including bronchial asthma), or a history of bronchospasm, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia
- Atrioventricular block
- Overt cardiac failure (see PRECAUTIONS).
- Cardiogenic shock.
- Hypersensitivity to any component of this product.

PRECAUTIONS

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.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (eg, 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.

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.

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 anesthetia 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 to 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.

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 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.

General
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 timolol maleate.

Pregnancy
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
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 children have not been established.

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
Attenuation 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
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.
The potential exists for hypotension, AV conduction disturbances, and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium blocker used. Dihydropyridine derivatives, such as nifédipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.
Intravenous calcium entry blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

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

SIDE EFFECTS

BLOCADREN is usually well tolerated in properly selected patients. Most side effects have been mild and transient.
Body as a whole: asthenia, fatigue, headache, chest pain, extremity pain, decreased exercise tolerance, weight loss.
Cardiovascular: bradycardia, cardiac arrest, cerebral vascular accident, palpitation, arrhythmia, AV block (2nd or 3rd degree), sinoatrial block, syncope, hypotension, edema, pulmonary edema, cardiac failure, Raynaud's phenomenon, cold hands and feet, claudication, worsening of arterial insufficiency, worsening of angina pectoris, vasodilatation.
Digestive: dyspepsia, nausea, vomiting, diarrhea, hepatomegaly.
Endocrine: hyperglycemia, hypoglycemia.
Integumentary: rash, pruritus, skin irritation, increased pigmentation, sweating, exfoliative dermatitis.
Musculoskeletal: arthralgia.
Nervous System: dizziness, vertigo, paresthesia, local weakness.
Psychiatric: nervousness, diminished concentration, hallucinations, nightmares, increased dreaming, insomnia, depression, somnolence, decreased libido.
Hematologic: non thrombocytopenic purpura.
Respiratory: dyspnea, bronchial spasm, rales, cough.
Special Senses: tinnitus, visual disturbances, diplopia, ptosis, eye irritation, dry eyes.
Urogenital: impotence, micturition difficulties.
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, and serum uric acid, and slight decreases in hemoglobin and hematocrit occurred, but were not progressive or associated with clinical manifestations.

AVAILABILITY

BLOCADREN is available in scored tablets containing 5, 10 or 15 mg each of timolol maleate, and intravenous injection 0.25 mg/ml of timolol maleate.

Manufactured in Zouk Mosbeh Lebanon by
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