Rx only

DUTOPROL™

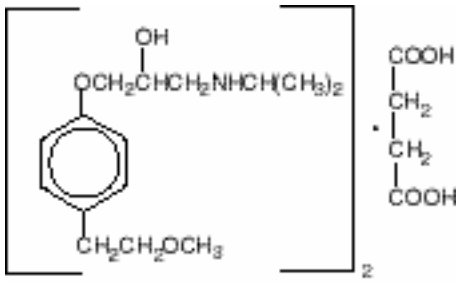
(metoprolol succinate extended release/hydrochlorothiazide)

TABLETS: 25/12.5 MG, 50/12.5 MG, AND
100/12.5 MG

DESCRIPTION

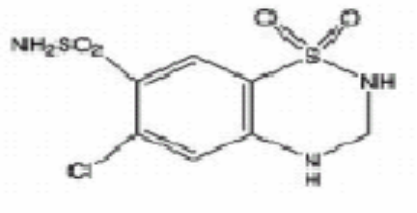
DUTOPROL™ (metoprolol succinate extended release /hydrochlorothiazide) combines a $beta_1$-selective (cardioselective) adrenoceptor blocking agent and a diuretic, hydrochlorothiazide.

Metoprolol succinate is chemically described as (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-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 is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

DUTOPROL is available for oral administration in 3 tablet strengths of metoprolol succinate extended release and hydrochlorothiazide.

DUTOPROL 25/12.5 contains 23.75 mg of metoprolol succinate extended release equivalent to 25 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide. DUTOPROL 50/12.5 contains 47.5 mg of metoprolol succinate extended release equivalent to 50 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide. DUTOPROL 100/12.5 contains 95 mg of metoprolol succinate extended release equivalent to 100 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide. The inactive ingredients of the tablets are silicon dioxide, ethylcellulose, hydroxypropyl cellulose, cornstarch, microcrystalline cellulose, polyvinyl pyrrolidone, sodium stearyl fumarate, hydroxypropyl methylcellulose, polyethylene glycol 6000, titanium dioxide, iron oxide (yellow), iron oxide (red) and paraffin.

CLINICAL PHARMACOLOGY

General

Metoprolol and hydrochlorothiazide have been used individually and in combination for the treatment of hypertension. The antihypertensive effects of these agents are additive.

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor-blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative $beta_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an E_{max} model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to $beta_1$-blockade. $Beta_1$-blocking effects in the range of 30–80% of the maximal effect (approximately 8–23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at higher plasma concentrations above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equimolar amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics

Metoprolol succinate extended release/hydrochlorothiazide

After single oral doses of DUTOPROL tablets, the peak plasma concentrations (C_{max}) of metoprolol and hydrochlorothiazide are observed within 10-12 hours and 2.0 hours of dose intake, respectively.

The rate and extent of absorption of metoprolol/ hydrochlorothiazide are similar in the fasting state and after a high-fat meal when given as DUTOPROL tablets. (See DOSAGE AND ADMINISTRATION.)

Single dose pharmacokinetics of metoprolol/hydrochlorothiazide given as DUTOPROL tablets is similar to that of each drug given individually as TOPROL-XL and a formulation of hydrochlorothiazide created for the clinical trial.

Metoprolol

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of immediate release metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration of immediate release metoprolol. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta blocking activity. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. (See DOSAGE AND ADMINISTRATION.)

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardioselectivity. (See PRECAUTIONS, Drug Interactions, Metoprolol.)

Metoprolol succinate extended release

The metoprolol component of DUTOPROL is bioequivalent to TOPROL-XL. In comparison to immediate release metoprolol, the plasma metoprolol levels following administration of TOPROL-XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of TOPROL-XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of immediate release metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of TOPROL-XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of immediate release metoprolol. Nevertheless, over the 24-hour dosing interval, $ß_1$-blockade is similar and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following TOPROL-XL administration.

Hydrochlorothiazide

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with a bioavailability of about 60-80%.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours (See DOSAGE AND ADMINISTRATION). The bioavailability of hydrochlorothiazide is not significantly affected by food following DUTOPROL administration.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

The mechanism of the antihypertensive effect of thiazide is unknown.

Clinical Trials

Metoprolol succinate extended release and hydrochlorothiazide

A randomized, double-blind, placebo-controlled, 8-week, unbalanced factorial study (N=1571) evaluated the antihypertensive effects of various doses of metoprolol succinate extended release (25, 50, 100 and 200 mg) and hydrochlorothiazide (6.25, 12.5 and 25 mg), and 9 of their combinations. The trial established that metoprolol succinate extended release and hydrochlorothiazide both contribute to the antihypertensive effect, change from baseline to week 8 in sitting diastolic ($p= 0.0015$) and systolic ($p=0.0006$) blood pressure). The predicted values for the drugs effects are shown in Table 1.

Blood pressure declines were apparent within 2 weeks and were maintained throughout the 8-week study. The blood pressure lowering 24 hours post dosing retained approximately 96% of the peak (6

hours post dosing) effect. The antihypertensive effect was similar regardless of age or gender, and the response to the metoprolol succinate extended release and hydrochlorothiazide combination appears similar in black and non-black patients.

Table 1. Placebo-corrected Predicted Values[a] for Change from Baseline in SBP/DBP

	TOPROL-XL Dosage				
HCT Dosage	**0 mg SBP/DBP**	**25 mg SBP/DBP**	**50 mg SBP/DBP**	**100 mg SBP/DBP**	**200 mg SBP/DBP**
0 mg	0/0	-2.0/-1.4	-3.7/-2.6	-6.1/-4.5	-7.0/-6.1
6.25 mg	-3.5/-1.9	-5.5/-3.3	-7.2/-4.5	-9.6/-6.4	-10.5/-8.0*
12.5 mg	-5.9/-3.3	-7.9/-4.7	-9.6/-5.9	-12.0/-7.8	-12.9/-9.3
25 mg	-7.7/-4.3	-9.7/-5.7*	-11.4/-6.9*	-13.8/-8.8	-14.7/-10.4

[a] Predicted values from a least-squares quadratic regression model.
*These doses were not studied.

INDICATIONS AND USAGE

Hypertension

DUTOPROL is indicated for the management of hypertension. The fixed-dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Metoprolol succinate extended release/hydrochlorothiazide is contraindicated in patients in cardiogenic shock, overt cardiac failure (see WARNINGS), second or third degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

WARNINGS

Metoprolol succinate extended release

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered DUTOPROL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, DUTOPROL or beta-blocking agent administration should be reinstated 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 DUTOPROL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$-selectivity, however, metoprolol succinate extended release/hydrochlorothiazide may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of DUTOPROL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol succinate is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: DUTOPROL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. (See PRECAUTIONS, General, Hydrochlorothiazide).

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.

Peripheral Vascular Disease: Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Calcium Channel Blockers: Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

Hydrochlorothiazide

Renal Disease: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION section).

Hepatic Disease: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. (See DOSAGE AND ADMINISTRATION section).

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, Lithium).

PRECAUTIONS

General

Metoprolol succinate extended release/hydrochlorothiazide

The precautions for the use of metoprolol succinate extended release/hydrochlorothiazide are the same as for the individual agents.

DUTOPROL should be used with caution in patients with impaired hepatic function. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent.

Metoprolol succinate extended release

Worsening cardiac failure may occur during up-titration of beta blockers. If such symptoms occur, diuretics should be increased and the dose of beta-blocking agent should not be advanced until clinical stability is restored. It may be necessary to lower the dose of DUTOPROL or temporarily discontinue it. (See WARNINGS.) Such episodes do not preclude subsequent successful titration of DUTOPROL.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, 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 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 after prolonged therapy. 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 (eg, 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. Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

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.

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

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Risk of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Information for Patients

Patients should be advised to take DUTOPROL regularly and continuously, as directed. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue DUTOPROL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with DUTOPROL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking DUTOPROL.

Drug Interactions

Metoprolol

Catecholamine-depleting drugs (eg, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

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

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics – Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin) – Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs – Additive effect or potentiation.

Cholestyramine and colestipol resins – 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.

Corticosteroids, ACTH – Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (eg, norepinephrine) – Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (eg, tubocurarine) – Possible increased responsiveness to the muscle relaxant.

Lithium – Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with DUTOPROL.

Non-steroidal Anti-inflammatory Drugs – 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 DUTOPROL and non-steroidal anti- inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Metoprolol / Hydrochlorothiazide
Carcinogenicity and mutagenicity studies have not been conducted with combinations of metoprolol and hydrochlorothiazide.

A combination of metoprolol tartrate and hydrochlorothiazide produced no adverse effects on the fertility and reproductive performance of male and female rats at doses of up to 200/50 mg/kg/day [about 10 and 20 times the maximum recommended human dose (MRHD) of metoprolol and hydrochlorothiazide, respectively, on a mg/m^2 basis].

Metoprolol
Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at oral dosage levels of up to 800 mg/kg/day (about 39 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at oral dosage levels of up to 750 mg/kg/day (about 18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

Genotoxicity tests performed on metoprolol tartrate (a dominant lethal mutation study in mice, chromosomal aberration studies in somatic cells, a *Salmonella* /mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella* /mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility was observed in a study in which metoprolol tartrate was administered to male and female rats at doses up to 500 mg/kg/day, about 25 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient.

Hydrochlorothiazide
Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses of up to 600 mg/kg/day (about 120 times the MRHD of 25 mg/day) or in male and female rats at doses of up to 100 mg/kg/day (about 40 times the MRHD). However, there was equivocal evidence of hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in the Ames bacterial mutagenicity test or the *in vitro* Chinese Hamster Ovary (CHO) test for chromosomal aberrations. Nor was it genotoxic *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, the Mouse Lymphoma Cell (mutagenicity) assay and the *Aspergillus* nidulans non-disjunction assay.

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/day (about 20 and 1.6 times the MRHD, on a mg/m^2 basis), respectively, prior to mating and throughout gestation.

Pregnancy
Pregnancy Category C
Metoprolol / Hydrochlorothiazide
Oral administration of metoprolol tartrate/hydrochlorothiazide combinations to pregnant rats during organogenesis at doses up to 200/50 mg/kg/day (10 and 20 times the MRHD for metoprolol and hydrochlorothiazide, respectively) or to pregnant rabbits at doses up to 25/6.25 mg/kg/day (about 2.5 and 5 times the MRHD for metoprolol and hydrochlorothiazide, respectively) produced no teratogenic effects. A 200/50 mg/kg/day metoprolol tartrate/hydrochlorothiazide combination administered to rats from mid-late gestation through lactation produced increased post-implantation loss and decreased neonatal survival.

There are no adequate and well-controlled studies in pregnant women. DUTOPROL should be used during pregnancy only if clearly needed.

Metoprolol
Metoprolol tartrate increased post-implantation loss and decreased neonatal survival in rats at a dose of 500 mg/kg/day, about 25 times the daily dose of 200 mg in a 60-kg patient, on a mg/m^2 basis. Similar effects were not observed at 50 mg/kg/day.

Hydrochlorothiazide
Hydrochlorothiazide administered to pregnant mice and rats during organogenesis at doses up to 3000 and 1000 mg/kg/day (600 and 400 times the MRHD), respectively, produced no harm to the fetus. Thiazides cross the placental barrier and appear in the cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and
possibly other adverse reactions which have occurred in the adult.

Nursing Mothers
Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or 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
Of the 849 subjects randomized to treatment with both metoprolol succinate extended release and hydrochlorothiazide in a factorial clinical study, 129 (15%) were 65 and over, while 16 (2%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. In addition, patients 70 to 84 years of age were studied in two clinical outcome trials (n=3025), which included a treatment regimen of a thiazide diuretic or beta blocker (metoprolol succinate extended release,

atenolol or pindolol) or their combination have not identified differences in responses between the elderly and younger patients.

Hydrochlorothiazide 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.

ADVERSE REACTIONS

Metoprolol succinate extended release /hydrochlorothiazide

The metoprolol succinate extended release and hydrochlorothiazide combination was evaluated for safety in 891 patients treated for hypertension in clinical trials. In a placebo-controlled trial, 843 patients were treated with various combinations of metoprolol succinate (doses of 25 to 200 mg) and hydrochlorothiazide (doses of 6.25 to 25 mg). Overall, the incidence of adverse experiences reported with the combination was comparable to placebo. Adverse events, whether or not attributed to treatment, occurring in greater than 1% of patients treated with DUTOPROL and at a rate equal to or greater than with placebo were: nasopharyngitis (3.4% vs 1.3%), fatigue (2.6% vs 0.7%), dizziness (2.6% vs 2.6%), back pain (1.7% vs 1.3%), and nausea (1.4% vs 0.7%). Adverse experiences were usually mild and transient in nature and infrequently required discontinuation of therapy (2.7% vs 2.6% with placebo).

Metoprolol

Most adverse effects have been mild and transient. The following adverse reactions have been reported for immediate release metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie’s disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The

oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to DUTOPROL.

Central 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).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Post-Marketing Experience

In addition, the following adverse reactions have been reported with metoprolol succinate in worldwide post-marketing use, regardless of causality:

Cardiovascular: 2nd and 3rd degree heart block.
Gastrointestinal: hepatitis, vomiting.
Hematologic: thrombocytopenia.
Musculoskeletal: arthralgia.
Nervous System/Psychiatric: anxiety/nervousness, hallucinations, paresthesia.
Reproductive, male: impotence.
Skin: increased sweating, photosensitivity, urticaria.
Special Sense Organs: taste disturbances.

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body As A Whole: weakness; *Cardiovascular*: hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs); *Digestive*: pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia; *Hematologic*: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity*: anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura; *Metabolic*: electrolyte imbalance, glycosuria; *Musculoskeletal*: muscle spasm; *Nervous System/Psychiatric*: Vertigo, paresthesias, dizziness, headache, restlessness; Renal: renal failure, renal dysfunction, interstitial nephritis; Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses*: transient blurred vision, xanthopsia; *Urogenital*: impotence.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were infrequently associated with the administration of DUTOPROL. The laboratory test findings with metoprolol or hydrochlorothiazide or their combination may include:

Creatinine, Blood Urea Nitrogen—Minor increases in blood urea nitrogen (BUN). (See WARNINGS, Renal Disease.)

Serum Electrolytes—Declines in serum potassium, sodium, chloride, magnesium. Increases in serum calcium and uric acid. (See PRECAUTIONS).

Glucose—Increase in serum or blood glucose. (See PRECAUTIONS, General, Hydrochlorothiazide.)

Lipids—Increase in serum total cholesterol, triglycerides. Decreases in high density lipoprotein (HDL).

Liver Function Tests—Increases in liver enzymes and/or serum bilirubin.

OVERDOSAGE

Metoprolol and Hydrochlorothiazide

The most frequently observed signs expected with overdosage of a beta-blocker are bradycardia and hypotension. Lethargy is also common, and with severe overdoses, delirium, coma, convulsions, and respiratory arrest have been reported to occur. Congestive heart failure, bronchospasm, and hypoglycemia may occur, particularly in patients with underlying conditions. With thiazide diuretics, acute intoxication is rare. The most prominent feature of overdose is acute loss of fluid and electrolytes. Signs and symptoms include cardiovascular (tachycardia, hypotension, shock), neuromuscular (weakness, confusion, dizziness, cramps of the calf muscles, paresthesia, fatigue, impairment of consciousness), gastrointestinal (nausea, vomiting, thirst) renal (polyuria, oliguria, or anuria [due to hemoconcentration]), and laboratory findings (hypokalemia, hyponatremia, hypochloremia, alkalosis, increased BUN [especially in patients with renal insufficiency]).

If overdosage of metoprolol and hydrochlorothiazide is suspected, the patient should be observed closely. Treatment is symptomatic and supportive; there is no specific antidote. Limited data suggest metoprolol is not dialyzable; similarly, there is no indication that hydrochlorothiazide is dialyzable. Suggested general measures include induction of emesis and/or gastric lavage, administration of activated charcoal, respiratory support, correction of fluid and electrolyte imbalance, and treatment of convulsions. Based on the expected pharmacologic actions and recommendations for other beta blockers and hydrochlorothiazide, the following measures should be considered when clinically warranted.

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension, Shock: The patient’s legs should be elevated. IV fluids should be administered and lost electrolytes (potassium, sodium) replaced. Intravenous glucagon may be useful. Vasopressors should be considered.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion or transvenous cardiac pacemaker insertion, as appropriate.

Congestive Heart Failure: Initiate conventional therapy (ie, digitalis, diuretics, vasodilating agents, inotropic agents).

Bronchospasm: Administer a bronchodilator such as isoproterenol and/or aminophylline

Hypoglycemia: Administer IV glucose.
Surveillance: Fluid and electrolyte balance (especially serum potassium) and renal function should be monitored until normalized.

DOSAGE AND ADMINISTRATION

Dosing must be individualized considering baseline and target blood pressure as well as experience with individual agents.

The side effects (see WARNINGS) of metoprolol succinate extended release are a mixture of dose-dependent phenomena (primarily bradycardia and fatigue); those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of metoprolol succinate extended release and hydrochlorothiazide will be associated with both sets of dose independent side effects. To minimize the known dose-related tolerability and safety-related effects of the individual agents, consideration should be given to initiating treatment at less than their maximum doses.

DUTOPROL may be administered with other antihypertensive agents.

DUTOPROL may be administered with or without food.

DUTOPROL is administered once daily.

Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.

Patients usually do not require doses in excess of 50 mg hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

The usual initial dose of metoprolol succinate extended release is 25 to 100 mg daily in a single dose.

Metoprolol succinate extended release doses greater than 400 mg have not been studied.

Replacement Therapy

DUTOPROL may be substituted for treatment with individual components.

Dose Titration by Clinical Effect

Use the dose necessary based on patient response once the need for combination product is established. Response rates are greater at higher doses.

Patients with insufficient blood pressure effects with metoprolol succinate extended release or hydrochlorothiazide alone may be switched to DUTOPROL.

The lowest DUTOPROL tablet available is 25/12.5 mg. A 50/6.25 mg dose can be achieved by splitting the 100/12.5 mg tablet. Subsequently titration may be carried out every 2 weeks up to a maximum of 200/25 mg (two DUTOPROL 100/12.5 mg tablets).

Patients with Renal Impairment

The usual regimens of therapy with DUTOPROL may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so DUTOPROL is not recommended.

Patients with Hepatic Impairment

The usual regimens of therapy with DUTOPROL may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of TOPROL-XL with lower doses of hydrochlorothiazide.

HOW SUPPLIED

DUTOPROL 25/12.5 (NDC 0186-1087-05)
yellow, circular, biconvex, film-coated tablet engraved with "A" above "IH" on one side, are supplied in bottles of 100.

DUTOPROL 50/12.5 (NDC 0186-1095-05)
light orange, circular, biconvex, film-coated tablet engraved with "A" above "IK" on one side, are supplied in bottles of 100.

DUTOPROL 100/12.5 (NDC 0186-1097-05)
yellow, circular, biconvex, film-coated tablet engraved with "A" above "IL" on one side and scored on the other side, are supplied in bottles of 100.

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.)

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