

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DUTOPROL safely and effectively. See full prescribing information for DUTOPROL.

**DUTOPROL® (metoprolol succinate extended release/ hydrochlorothiazide) tablets, for oral use**  
Initial U.S. Approval: 2006

-----INDICATIONS AND USAGE-----

DUTOPROL is the combination tablet of metoprolol succinate, a beta adrenoceptor blocker and hydrochlorothiazide (HCTZ), a thiazide diuretic, indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

-----DOSAGE AND ADMINISTRATION-----

- Usual dose range: Hydrochlorothiazide 12.5 to 25 mg and metoprolol succinate 25 to 200 mg dosed once daily. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets (metoprolol succinate/HCTZ mg): 25/12.5 mg, 50/12.5 mg, 100/12.5 mg. (3)

-----CONTRAINDICATIONS-----

- Hypersensitivity to metoprolol succinate or hydrochlorothiazide or other sulfonamide-derived drugs. (4)
- Cardiogenic shock or decompensated heart failure. (4)
- Sinus bradycardia, sick sinus syndrome, and greater than first-degree block unless a permanent pacemaker is in place. (4)
- Anuria. (4)

-----WARNINGS AND PRECAUTIONS-----

- Abrupt cessation may exacerbate myocardial ischemia. (5.1)
- May worsen congestive heart failure. (5.2)
- Bronchospasm: Avoid beta-blockers. (5.3)
- Bradycardia. (5.4) Avoid discontinuing therapy prior to major surgery. (5.5) May mask symptoms of hypoglycemia. (5.6)
- Monitor serum electrolytes and creatinine periodically. (5.7)

- Peripheral vascular disease: Can aggravate symptoms of arterial insufficiency. (5.9)
- Pheochromocytoma: First initiate therapy with an alpha blocker. (5.10)
- Abrupt withdrawal in thyrotoxicosis might precipitate a thyroid storm. (5.11)

-----ADVERSE REACTIONS-----

Adverse events which occurred greater than 1% more frequently in patients treated with DUTOPROL than placebo were: nasopharyngitis and fatigue. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Concordia Pharmaceuticals Inc. at 1-877-370-1142 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

-----DRUG INTERACTIONS-----

- Catecholamine-depleting drugs (e.g., MAO inhibitors): Hypotension, bradycardia. (7.1)
- Patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (7.1) CYP2D6 inhibitors: Increased metoprolol concentration. (12.3)
- Digitalis glycosides, clonidine, diltiazem and verapamil: Bradycardia. (5.4, 7.1)
- Clonidine: Rebound hypertension following clonidine withdrawal. (7.1)
- Antidiabetic drugs: Dosage adjustment may be required. (7.2)
- Cholestyramine and colestipol: Reduced absorption of thiazides. (7.2)
- Lithium: Risk of lithium toxicity. (7.2)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Reduced diuretic, natriuretic, and antihypertensive effects of diuretics. (7.2)

-----USE IN SPECIFIC POPULATIONS-----

- Hepatic Impairment: Consider initiating metoprolol succinate therapy at low doses and gradually increase dosage to optimize therapy, while monitoring closely for adverse events. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

DUTOPROL is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including metoprolol and hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

DUTOPROL may be administered with other antihypertensive agents.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosing Information

The recommended starting dose of DUTOPROL (metoprolol succinate extended release and hydrochlorothiazide) is 25 mg/12.5 mg taken orally once daily with or without food. Depending on the blood pressure response, the dose may be titrated at intervals of 2 weeks to a maximum recommended dose of 200 mg/25 mg (two DUTOPROL 100 mg/12.5 mg tablets) once daily [*see Clinical Studies (14)*].

### **3 DOSAGE FORMS AND STRENGTHS**

25/12.5 mg tablets: Yellow, circular, biconvex, film-coated tablet engraved with “A” above “IH” on one side.

50/12.5 mg tablets: Light orange, circular, biconvex, film-coated tablet engraved with “A” above “IK” on one side.

100/12.5 mg tablets: Yellow, circular, biconvex, film-coated tablet engraved with “A” above “IL” on one side and scored on the other side.

### **4 CONTRAINDICATIONS**

DUTOPROL is contraindicated in patients with:

- Cardiogenic shock or decompensated heart failure.
- Sinus bradycardia, sick sinus syndrome, and greater than first-degree block unless a permanent pacemaker is in place.
- Anuria
- Hypersensitivity to metoprolol succinate or hydrochlorothiazide or to other sulfonamide-derived drugs.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Abrupt Cessation of Therapy**

Following abrupt cessation of therapy with beta adrenergic blockers, exacerbations of angina pectoris and myocardial infarction may occur. When discontinuing chronically administered DUTOPROL, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly resume therapy and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician’s advice. Because coronary artery disease is common and may be unrecognized, avoid abrupt discontinuation of DUTOPROL in patients treated only for hypertension.

#### **5.2 Heart Failure**

Worsening cardiac failure may occur during up-titration of beta-blockers. If such symptoms occur, increase diuretics and restore clinical stability (compensated heart failure) before advancing the dose of DUTOPROL [*see Dosage and Administration (2)*]. It may be necessary to lower the dose of DUTOPROL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of DUTOPROL.

#### **5.3 Bronchospasm**

Beta adrenergic blockers can cause bronchospasm. Patients with bronchospastic disease should, in general, not receive beta adrenergic blockers. Because of its relative beta<sub>1</sub> cardio-selectivity, however, metoprolol-containing products including DUTOPROL may be used in patients with bronchospastic disease who do not respond to or cannot tolerate other antihypertensive treatment. Because beta<sub>1</sub>-selectivity is not absolute, in such patients use the lowest possible DUTOPROL dose and have bronchodilators (e.g., beta<sub>2</sub>-agonists) readily available or administer concomitantly.

#### **5.4 Bradycardia**

Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of Dutoprol. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff-Parkinson-White) or on concomitant drugs that cause bradycardia [see *Drug Interactions (7.1)*] may be at increased risk. Monitor heart rate in patients receiving Dutoprol. If severe bradycardia develops, reduce or stop Dutoprol.

#### **5.5 Risks of Use in Major Surgery**

Avoid initiation of high-dose regimen of DUTOPROL in patients with cardiovascular risk factors undergoing non-cardiac surgery, since use in such patients has been associated with bradycardia, hypotension, stroke and death.

Chronically administered beta adrenergic blockers should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures [see *Warnings and Precautions (5.1)*].

#### **5.6 Masked Signs of Hypoglycemia**

Beta adrenergic blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

#### **5.7 Electrolyte and Metabolic Effects**

DUTOPROL contains hydrochlorothiazide which can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide reduces clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

#### **5.8 Renal Impairment**

Patients with chronic kidney disease, severe heart failure, or volume depletion may be at increased risk for developing acute renal failure on drugs containing hydrochlorothiazide, including DUTOPROL.

#### **5.9 Peripheral Vascular Disease**

Beta adrenergic blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

#### **5.10 Pheochromocytoma**

If DUTOPROL is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

#### **5.11 Thyrotoxicosis**

Beta adrenergic blockers may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of a beta adrenergic blocker may precipitate a thyroid storm.

### 5.12 Anaphylactic Reaction

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

### 5.13 Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause acute transient myopia and acute angle-closure glaucoma (idiosyncratic reactions). Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of hydrochlorothiazide initiation. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Untreated acute angle-closure glaucoma can lead to permanent vision loss. Given that DUTOPROL contains hydrochlorothiazide, if these symptoms occur, discontinue DUTOPROL. Consider prompt medical or surgical treatment if the intraocular pressure remains uncontrolled.

### 5.14 Exacerbation of Systemic Lupus Erythematosus

Hydrochlorothiazide can exacerbate or activate systemic lupus erythematosus.

## 6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in labeling:

- Worsening angina or myocardial infarction. [see *Warnings and Precautions (5)*]
- Worsening heart failure. [see *Warnings and Precautions (5)*]
- Worsening A V block. [see *Contraindications (4)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

#### *Metoprolol succinate extended release/hydrochlorothiazide*

The metoprolol succinate extended release and hydrochlorothiazide combination was evaluated for safety in 891 patients with hypertension in clinical trials. In a randomized, double-blind, placebo-controlled, factorial trial (Study 1), 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) [see *Clinical Studies (14)*]. Adverse events which occurred more than 1% more frequently in patients treated with DUTOPROL than placebo were: nasopharyngitis (3.4% vs 1.3%) and fatigue (2.6% vs 0.7%).

The adverse reactions of metoprolol succinate extended release are a mixture of dose-dependent phenomena (primarily bradycardia and fatigue) and 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 DUTOPROL will be associated with both sets of dose independent reactions.

#### Laboratory Abnormalities

*Liver Enzyme Tests*—Increases in liver enzymes or serum bilirubin.

## 6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of DUTOPROL, metoprolol succinate extended release, and/or hydrochlorothiazide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

### *Metoprolol*

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

*Central Nervous System:* Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia, dizziness

*Cardiovascular:* Shortness of breath, bradycardia, cold extremities; arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain, hypotension.

*Respiratory:* Dyspnea, wheezing (bronchospasm).

*Gastrointestinal:* Diarrhea, nausea, dry mouth, gastric pain, constipation, flatulence, heartburn, hepatitis, vomiting.

*Hypersensitivity Reactions:* Pruritus, rash

*Miscellaneous:* Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance, depression.

Potential Adverse Reaction: In addition, adverse reactions not listed above, that have been reported with other beta-adrenoceptor blockers 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, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

*Hematologic:* Non-thrombocytopenic purpura, thrombocytopenic purpura, agranulocytosis.

*Hypersensitivity Reactions:* Laryngospasm, and respiratory distress

### *Hydrochlorothiazide*

Adverse reactions that have been reported with hydrochlorothiazide are listed below:

*Body as a Whole:* Weakness

*Cardiovascular:* Orthostatic hypotension

*Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia

*Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

*Hypersensitivity Reactions:* Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria

*Metabolic:* Glycosuria

*Musculoskeletal:* Muscle spasm

*Nervous System/Psychiatric:* Vertigo, paresthesias, restlessness

*Renal:* Interstitial nephritis

*Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

*Special Senses:* Transient blurred vision, xanthopsia

### **Non-melanoma Skin Cancer**

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of  $\geq 50,000$ mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

## **7 DRUG INTERACTIONS**

### **7.1 Drug Interactions with Metoprolol**

#### *Catecholamine Depleting Drugs:*

The concomitant use of catecholamine-depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) with beta adrenergic blockers may have an additive affect and increase the risk of hypotension or bradycardia

#### *CYP2D6 Inhibitors:*

Drugs that are strong inhibitors of CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone were shown to double metoprolol concentrations. While there is no information about moderate or weak inhibitors, these too are likely to increase metoprolol concentration. Increases in plasma concentration decrease the cardioselectivity of metoprolol [see *Clinical Pharmacology (12.3, 12.5)*]. Monitor patients closely, when the combination cannot be avoided.

#### *Digitalis, Clonidine, and Calcium Channel Blockers:*

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

## 7.2 Drug Interactions with Hydrochlorothiazide

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

*Ion exchange 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%, respectively. Stagger the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine and colestipol resins) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins to minimize the interaction.

*Lithium:* Diuretics reduce the renal clearance of lithium and increase the risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use.

*Non-Steroidal Anti-Inflammatory Drugs:* NSAIDs can reduce the diuretic, natriuretic, and antihypertensive effects of thiazide diuretics.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Untreated hypertension during pregnancy can lead to adverse outcomes for the mother and the fetus (*see Clinical Considerations*). Available data from published observational studies have not demonstrated a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with metoprolol use during pregnancy. However, there are inconsistent reports of intrauterine growth restriction, preterm birth, and perinatal mortality with maternal use of beta blockers, including metoprolol, during pregnancy (*see Data*). There have been rare reports of jaundice, thrombocytopenia, and electrolyte imbalances in infants exposed to thiazide medications during pregnancy.

In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages up to 24 times, on a mg/m<sup>2</sup> basis, the daily dose of 200 mg in a 60-kg patient. The combination of metoprolol tartrate/hydrochlorothiazide administered to rats from mid-late gestation through lactation also produced increased post-implantation loss and decreased neonatal survival (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major malformations and miscarriage in clinically recognized pregnancies is 2-4%, and 15-20%, respectively.

#### Clinical Considerations

##### *Disease-Associated Maternal and/or Embryo/Fetal Risk*



Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

### *Fetal/Neonatal Adverse Reactions*

#### Metoprolol

Neonates born to mothers who are receiving metoprolol during pregnancy may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates for symptoms of hypotension, hypoglycemia, bradycardia, and respiratory depression and manage accordingly.

### Data

#### *Human Data*

Data from published observational studies did not demonstrate an association of major congenital malformations and the use of either metoprolol or hydrochlorothiazide in pregnancy. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth and perinatal mortality with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

#### *Animal Data*

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 on a mg/m<sup>2</sup> basis 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 on a mg/m<sup>2</sup> basis 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.

#### Metoprolol

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 24 times, on a mg/m<sup>2</sup> basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

#### 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 on a mg/m<sup>2</sup> basis), respectively, produced no harm to the fetus. Thiazides cross the placental barrier and appear in the cord blood.

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of DUTOPROL in human milk, the effects on the breastfed infant, or the effects on milk production. However, data are available on the individual components of DUTOPROL. Available data from published literature on metoprolol and hydrochlorothiazide report that each drug is present in human milk (*see Data*). There are no reports of adverse effects on breastfed infants exposed to metoprolol or hydrochlorothiazide during lactation. Doses of hydrochlorothiazide associated with clinically significant diuresis have been associated with impaired milk production. There is no information regarding the effects of metoprolol on milk production. Monitor infants exposed to DUTROPROL through breastmilk for drowsiness or poor feeding (*see Clinical Considerations*).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUTOPROL and any potential adverse effects on the breastfed child from DUTOPROL or from the underlying maternal condition.

### Clinical Considerations

#### *Monitoring for adverse reactions*

Monitor the breastfed infant for bradycardia and other symptoms of beta blockade such as listlessness (hypoglycemia).

### Data

#### Metoprolol

Based on published case reports, the estimated daily infant dose of metoprolol received from breastmilk ranged from 0.05 mg to less than 1 mg. The estimated relative infant dosage was 0.5% to 2% of the mother's weight-adjusted dosage.

In two women who were taking unspecified amount of metoprolol, milk samples were taken after one dose of metoprolol. The estimated amount of metoprolol and alpha-hydroxymetoprolol in breast milk is reported to be less than 2% of the mother's weight-adjusted dosage.

In a small study, breast milk was collected every 2 to 3 hours over one dosage interval, in three mothers (at least 3 months postpartum) who took metoprolol of unspecified amount. The average amount of metoprolol present in breast milk was 71.5 mcg/day (range 17.0 to 158.7). The average relative infant dosage was 0.5% of the mother's weight-adjusted dosage.

#### Hydrochlorothiazide

A single study involving one woman and her infant showed a peak concentration of 275 mcg/L at 3 hours following 50 mg dose. No drug was detected (< 20 mcg/L) in the infant's plasma at 2 and 11 hours following mother's dose.

## **8.3 Females and Males of Reproductive Potential**

### Infertility

#### *Males*

Based on the published literature, beta blockers (including metoprolol) may cause erectile dysfunction and inhibit sperm motility. No evidence of impaired fertility due to metoprolol or hydrochlorothiazide was observed in rats [see *Nonclinical Toxicology (13.1)*].

#### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

#### **8.5 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 adrenergic 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.

#### **8.6 Hepatic Impairment**

##### ***Metoprolol***

No studies have been performed with metoprolol succinate in patients with hepatic impairment. Because metoprolol succinate is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

##### ***Hydrochlorothiazide***

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

### **10 OVERDOSAGE**

#### **10.1 Signs and Symptoms**

The most frequently observed signs expected with overdosage of a beta adrenergic blocker are bradycardia and bradyarrhythmia, hypotension, heart failure, cardiac conduction disturbances and bronchospasm, atrioventricular block, hypoxia, impairment of consciousness/coma, cardiogenic shock, nausea and vomiting.

With thiazide diuretics, acute intoxication is rare. The most prominent feature of overdose is acute loss of fluid, electrolytes and magnesium. Signs and symptoms of overdose may include hypotension, dizziness, muscle cramps, renal impairment or failure, and sedation/ impairment of consciousness. Altered laboratory findings can also occur (e.g. hypokalemia, hypomagnesaemia, hyponatremia, hypochloremia, alkalosis, increased BUN).

#### **10.2 Management**

Care should be provided at a facility that can provide appropriate supporting measures, monitoring and supervision as treatment is symptomatic and supportive and there is no specific antidote. Limited data

suggest that neither metoprolol nor hydrochlorothiazide is dialyzable. If justified, gastric lavage and/or activated charcoal can be administered.

Based on the expected pharmacologic actions and recommendations for other beta adrenergic blockers and hydrochlorothiazide, the following measures should be considered when clinically warranted.

Hemodialysis is unlikely to make a useful contribution to metoprolol elimination [see *Clinical Pharmacology* (12.3)].

*Bradycardia and conduction disturbances:* Use atropine, adrenergic-stimulating drugs or pacemaker.

*Hypotension or shock:* Treat underlying bradycardia. Consider intravenous expansion, vasopressors, , injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), or intravenous administration of adrenergic drugs such as dobutamine,

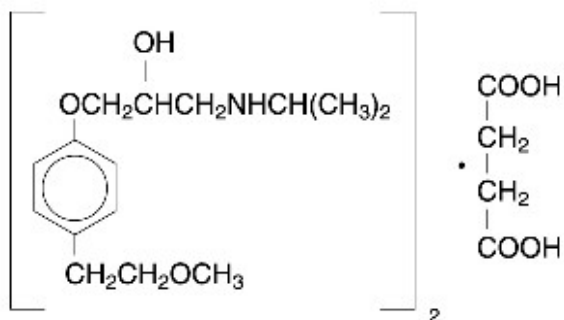
*Heart failure :* Treat bradycardia if present and support hemodynamics with inotropes if necessary.

*Bronchospasm:* Can usually be reversed by bronchodilators.

## 11 DESCRIPTION

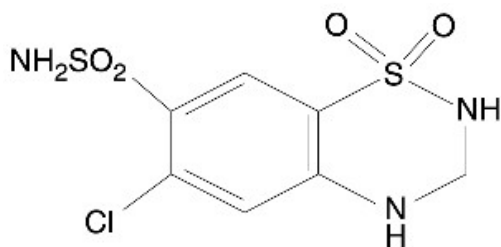
DUTOPROL® (metoprolol succinate extended release/hydrochlorothiazide) combines a beta adrenoceptor blocker and a thiazide diuretic.

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, and 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<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub> 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 for oral administration supplied 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.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Metoprolol is a beta<sub>1</sub>-selective (cardioselective) adrenergic receptor blocker. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta<sub>2</sub>-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.

The relative beta<sub>1</sub>-selectivity of metoprolol is demonstrated by the following: (1) In healthy subjects, metoprolol is unable to reverse the beta<sub>2</sub>-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<sub>1</sub> and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta<sub>1</sub>-receptor blocking doses.

The mechanism of the antihypertensive effects of beta adrenergic blockers 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 diuretics is unknown.

### 12.2 Pharmacodynamics

*Metoprolol*

Clinical pharmacology studies have confirmed the beta adrenergic blocker activity of metoprolol, 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 relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Beta<sub>1</sub>-blocking effects in the range of 30–80% of the maximal effect (approximately 8 to 23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30 to 540 nmol/L. The relative beta<sub>1</sub>-selectivity of metoprolol diminishes and blockade of beta<sub>2</sub>-adrenoceptors increases at higher plasma concentrations above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of hypertension 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<sub>2</sub>-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*

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.

## **12.3 Pharmacokinetics**

### *Metoprolol/hydrochlorothiazide*

After single oral doses of DUTOPROL, plasma levels of metoprolol and of hydrochlorothiazide are similar to levels obtained after single doses of TOPROL XL and hydrochlorothiazide. Peak plasma concentrations (C<sub>max</sub>) of metoprolol and hydrochlorothiazide occur within 10-12 hours and 2 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 after administration of DUTOPROL.

### *Metoprolol*

#### *Absorption*

Absorption of metoprolol is complete following oral administration. The absolute bioavailability of metoprolol after oral administration of immediate release metoprolol is estimated to be about 50% because of pre-systemic metabolism (first-pass metabolism). Plasma levels achieved are highly variable after oral administration of immediate release metoprolol.

#### *Distribution*

Metoprolol is known to cross the blood brain barrier following oral administration and CSF concentrations close to that observed in plasma have been reported. About 12% of the drug is bound to human serum albumin.

#### *Elimination*

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours.

#### *Metabolism*

Metoprolol is primarily metabolized by CYP2D6. Metoprolol is a racemic mixture of R- and S-enantiomers, and when administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. CYP2D6 is absent (poor metabolizers) in about 8% of Caucasians and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Concomitant use with CYP2D6 inhibitors or administration of metoprolol in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardioselectivity [*see Drug Interactions (7.2)*].

#### *Excretion*

Less than 5% of an oral dose and 10% of an intravenous 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. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in healthy subjects.

*Pharmacokinetic drug interactions:* 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. 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.

#### *Hydrochlorothiazide*

The pharmacokinetics of hydrochlorothiazide is dose proportional in the range of 12.5 to 75 mg.

The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations ( $C_{max}$ ) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Hydrochlorothiazide binds to albumin (40 to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours.

About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

*Pharmacokinetic drug interactions:* Absorption of hydrochlorothiazide is impaired in the presence of ionic 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%, respectively.

## **12.5 Pharmacogenomics**

CYP2D6 is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by several drugs. Poor metabolizers of CYP2D6 will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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<sup>2</sup> 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 (41 times, on a mg/m<sup>2</sup> basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring 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 three oral dosage levels of up to 750 mg/kg/day (about 18 times, on a mg/m<sup>2</sup> 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.

All genotoxicity tests performed with metoprolol tartrate (a dominant lethal study in mice, chromosomal 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 of metoprolol tartrate performed in rats at doses up to 22 times, on a mg/m<sup>2</sup> 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 on a mg/m<sup>2</sup> basis) or in male and female rats at doses of up to 100 mg/kg/day (about 40 times the MRHD on a mg/m<sup>2</sup> basis). 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<sup>2</sup> basis), respectively, prior to mating and throughout gestation.

## 14 CLINICAL STUDIES

A randomized, double-blind, placebo-controlled, 8-week, factorial study (Study 1) (N=1571) evaluated the antihypertensive effects of various doses (given once daily) 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 contributed to the antihypertensive effect, as measured by the 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.

**Table 1. Placebo-corrected Change from Baseline\* in SBP/DBP at Week 8 in Study 1**

		Metoprolol				
		0 mg	25 mg	50 mg	100 mg	200 mg
HCTZ	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 <sup>†</sup>
	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 <sup>†</sup>	-11.4/-6.9 <sup>†</sup>	-13.8/-8.8	-14.7/-10.4

\*Predicted values from a least-squares quadratic regression model.

<sup>†</sup>These doses were not studied.

SBP = systolic blood pressure; DBP = diastolic blood pressure

Blood pressure declines were apparent within 2 weeks and were maintained throughout the 8-week study. The blood pressure lowering effect 24 hours post-dosing retained approximately 96% of the peak effect (6 hours post-dosing). The antihypertensive effect was similar regardless of age or gender, and the blood pressure response to the metoprolol succinate extended release and hydrochlorothiazide combination appears similar in black and non-black patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

DUTOPROL is supplied as circular, biconvex, film-coated tablets engraved on one side.

Metoprolol/ Hydrochlorothiazide	Engraving	Scored	NDC 59212-xxx-xx
			Bottle/30
25/12.5 mg	A IH	No	087-30
50/12.5 mg	A IK	No	095-30
100/12.5 mg	A IL	Yes	097-30

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

## 17 PATIENT COUNSELING INFORMATION

### **Avoid Abrupt Discontinuation**

Advise patients to take DUTOPROL regularly and continuously, as directed. If a dose is missed, instruct the patient to take only the next scheduled dose (without doubling the dose). Instruct patients not to interrupt or discontinue DUTOPROL without consulting a healthcare provider. *[See Warnings and Precautions (5.1)].*

### **Non-melanoma Skin Cancer**

Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

### **Bronchospasm**

Inform patients that beta adrenergic blockers can cause bronchospasm and to inform their healthcare providers if they start to wheeze or have difficulty breathing. *[See Warnings and Precautions (5.3)].*

### **Electrolyte Changes**

Inform patients that they may need blood tests to monitor their serum electrolytes. *[See Warnings and Precautions (5.7)].*

### **Acute Myopia and Secondary Angle-Closure Glaucoma**

Inform patients to report decreased visual acuity or ocular pain and to stop DUTOPROL and contact their healthcare provider right away if these symptoms occur. *[See Warnings and Precautions (5.13)].*

### **Hypersensitivity Reaction**

Instruct patients that hypersensitivity reactions to DUTOPROL may occur. *[See Contraindications (4)].*

### **Lithium Toxicity**

Instruct patients to inform other doctors that they are taking a diuretic. *[See Drug Interactions (7.2)].*

### **Lactation**

Advise patients who are breastfeeding to monitor their infants for signs of bradycardia and other symptoms of beta blockade such as listlessness (hypoglycemia). *[see Use in Specific Populations (8.2)].*

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Concordia Pharmaceuticals Inc.  
St. Michael, Barbados BB11005

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