

# AstraZeneca introduces two new product security features



Please see brief summary of full Prescribing Information including boxed WARNING on adjacent page.

Please see brief summary of full Prescribing Information including boxed WARNING regarding abrupt cessation of therapy on adjacent page.

**Counterfeit drugs threaten the health and well-being of patients worldwide. To verify the authenticity of AstraZeneca products, two new product security features will be introduced to our packaging:**

1.



A color-shift security logo on the bottle's label and unit dose cartons.

2.



A color-shift security logo on the bottle's induction seal to deter tampering with the bottle's contents.

**The features mentioned above change from GREEN to PURPLE when viewed at different angles.**

The new product security features will be used in packaging for SEROQUEL® (quetiapine fumarate), TOPROL-XL® (metoprolol succinate), and ARIMIDEX® (anastrozole), followed by NEXIUM® (esomeprazole magnesium), PULMICORT RESPULES® (budesonide inhalation suspension), and CRESTOR® (rosuvastatin calcium).

To view a list of products that has received the new product security packaging features, please see the product security Web site at <http://www.astrazeneca-us.com/content/products/safety/prof.asp> or call the AstraZeneca Information Center at **1-800-236-9933**.

AstraZeneca may change the features and/or labeling on a periodic basis.

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***Patient safety is an extremely important issue to AstraZeneca. With the ongoing risk of counterfeit products being introduced into the supply chain, the color-shift logos were developed to protect the authenticity of AstraZeneca products and the safety of the patients who depend on them.***

## FAQs

### **What are counterfeit drugs?**

Counterfeit drugs are sold under a product name without proper authorization. Counterfeiting, which can apply to both brand name and generic drugs, means that a product is deliberately and fraudulently labeled in a way that suggests that it is the authentic, approved product made by an authorized manufacturer.

### **What are the potential dangers of counterfeit drugs to patients?**

Counterfeit drugs pose hazards to patients in many ways. They may contain the wrong active ingredients, improper doses of the active ingredients, inert substances, or even harmful and unregulated ingredients. A patient who takes a counterfeit medication may be at risk for allergic reactions, unexpected side effects, or worsening of his/her current medical conditions. Counterfeit drugs are unlikely to be as effective as genuine products, and, in the worst cases, these drugs may be hazardous to human health, or even fatal.

### **Why is AstraZeneca employing a color-shift logo in their packaging?**

Patient safety is an extremely important issue to AstraZeneca. With the ongoing risk of counterfeit products being introduced into the supply chain, the color-shift logos were developed to protect the authenticity of AstraZeneca products and the safety of the patients who depend on them.

### **How do the color-shift logos work?**

View the AstraZeneca color-shift security logos in a well-lit area. To see the color-shift logo on the label, hold the bottle horizontally. As you rotate the bottle away from you slightly, you will see the logo in the lower right-hand corner of the label change color from green to purple. To see the color-shift logo on the induction seal, remove the cap of the bottle, and hold the bottle vertically upright. Tilt the bottle away from you slightly, and you will notice the seal's logo change color from green to purple.

### **What if an AstraZeneca bottle does not have a color-shift logo?**

It will take some time to deplete existing inventory of AstraZeneca products already in distribution, manufactured prior to the introduction of the color-shift logo packaging. Additionally, not all AstraZeneca products will receive the new security packaging simultaneously. Therefore, some authentic AstraZeneca products will still be available without the security color-shift logos. To minimize the risk of obtaining counterfeit AstraZeneca products, purchase them from an AstraZeneca authorized distributor. For a current list of authorized AstraZeneca distributors, please see the *product security for pharmacy professions* section of our Web site at <http://www.astrazeneca-us.com/content/products/safetyprof.asp> or call the AstraZeneca Information Center at 1-800-236-9933 or by e-mail at [information.center@astrazeneca.com](mailto:information.center@astrazeneca.com)

### **What do I do if I think I may have purchased a counterfeit AstraZeneca product?**

If you suspect that an AstraZeneca product you have purchased may be counterfeit, please contact the AstraZeneca Information Center at 1-800-236-9933. If you have additional questions, please visit the AstraZeneca Web site at <http://www.astrazeneca-us.com/> or call the AstraZeneca Information Center at 1-800-236-9933 or by e-mail at [information.center@astrazeneca.com](mailto:information.center@astrazeneca.com)

*If you would like additional information regarding AstraZeneca products, please contact the Information Center at AstraZeneca in the United States at 1-800-236-9933, Monday through Friday, 8 AM to 7 PM EST, excluding holidays.*

**BRIEF SUMMARY** of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**  
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seven placebo-controlled trials (total duration of 10 weeks) revealed that the relative risk of death was 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

**INDICATIONS AND USAGE: Bipolar Mania.** SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia.** SEROQUEL is indicated for the long-term treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**CONTRAINDICATIONS:** SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

**WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). **Neuroleptic Malignant Syndrome (NMS).** A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, increased muscle rigidity, autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia), and additional signs may include elevated creatine phosphokinase, myoglobinuria (myoglobinuria) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central nervous system infections and drug fever. **Discontinuation of Antipsychotic Drugs and Other Drugs not Essential to Concomitant Therapy.** 2) Intensive symptomatic treatment and medical monitoring; and 3) general management of any concomitant serious medical problems for which specific treatments are available; there is no general agreement about specific pharmacologic treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinitiation of drug therapy should be carefully considered. The patient should be carefully monitored because of the recurrence of NMS. **Orthostatic Hypotension.** Tardive Dyskinesia. Antipsychotic drugs have the potential to cause tardive dyskinesia, which is generally irreversible and associated with long-term use of the drug. The syndrome is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest doses and the shortest duration of treatment providing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hyperglycemia and Diabetes Mellitus.** Hyperglycemia, in some cases extreme and associated with ketacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these concerns, the relationship between atypical antipsychotic use and increased risk of diabetes mellitus is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, hypertension, dyslipidemia, and a family history of diabetes mellitus) should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, continuation of therapy has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite drug discontinuation.

**PRECAUTIONS: General: Orthostatic Hypotension.** SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha_1$ -adrenergic antagonist properties. Syncope was reported in 1% (23/2667) of the patients treated with SEROQUEL compared to 0% (0/607) on placebo and about 0.4% (25/227) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts.** The development of cataracts was observed in association with quetiapine treatment in chronic dose studies (see Animal Toxicology). Lens changes have also been observed in patients treated with long-term SEROQUEL. In patients with preexisting cataracts, the possibility of further lens changes is possible. Nevertheless, the possibility of lens changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam and/or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment. **Seizures.** During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (14/227) on active control drugs. As with other antipsychotics, SEROQUEL should be used with caution in patients with a history of seizures. **Electrolytes.** Treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL-treated patients compared to 7% (15/203) of placebo-treated patients had elevated TSH levels. Of the SEROQUEL-treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglycerides.** In schizophrenia trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia.** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of prolactin-dependent rat mammary gland tumors are normally responsive to prolactin. The prescription of these drugs is complicated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations.** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 2 weeks of drug treatment and normally returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment.** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL, especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 18% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 14% of patients on SEROQUEL compared to 4% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL (including doses not affecting their activities). **Pharmacokinetics.** One case of pruritus in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to cause pruritus. It is possible that SEROQUEL may have similar effects. Treatment options may require surgical intervention. **Body Temperature Regulation.** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may

contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Psychopharmacology: Psychopharmacology and Aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. Suicide.** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness.** Patient response with SEROQUEL may be altered by other concomitant medications if the risk is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension.** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration and at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance.** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL (including doses not affecting their activities) will not adversely affect their activities. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Laboratory Tests:** No specific laboratory tests are indicated for patients receiving SEROQUEL. **Other Medications:** Patients should be advised that other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine:** Phenylalanine administration of quetiapine (25 mg bid) and phenylalanine (100 mg bid) increased the mean plasma concentration of quetiapine 4-fold. **Effect of Quetiapine on Other Drugs:** Quetiapine (250 mg bid) did not appear to affect the maintenance of clinical effects of quetiapine and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glaucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate). **Divalproex:** Co-administration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) did not affect the oral clearance of quetiapine (250 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg bid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A4 Inhibitors:** Co-administration of ketoneczone (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoneczone and other inhibitors of cytochrome P450 3A (eg, macrolides, fluconazole, and erythromycin). **Phenylethylamine:** Haloperidol and Risperidone: Co-administration of fluoxetine (60 mg once daily), imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs: Lorazepam:** The mean oral clearance of lorazepam (2 mg single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg bid steady state. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when quetiapine (150 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid administered as divalproex (500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg bid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Selected Psychotropic Disorders:** There is no clinically relevant effect on the clearance of antipsychotic or antipsychotic agents. **Antipsychotics:** Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychotropic disorders had no clinically relevant effect on the clearance of antipsychotic or antipsychotic agents. **Antipsychotics:** Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychotropic disorders had no clinically relevant effect on the clearance of antipsychotic or antipsychotic agents. **Antipsychotics:** Administration of multiple daily doses up to 750 mg/day (on a bid schedule) of quetiapine to subjects with selected psychotropic disorders had no 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Please read this summary carefully and then ask your doctor about TOPROL-XL. Do not stop treatment without first talking with your doctor. No advertisement can provide all the information needed to determine if a drug is right for you. This advertisement does not take the place of careful discussions with your doctor. Only your doctor has the training to weigh the risks and benefits of a prescription drug.



**ONCE-A-DAY**  
**TOPROL-XL®**  
(metoprolol succinate) extended-release tablets  
25 mg  
50 mg  
100 mg  
200 mg

**BRIEF SUMMARY:** For full Prescribing Information, see package insert.  
**INDICATIONS AND USAGE**

**Hypertension:** TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.  
**Angina Pectoris:** TOPROL-XL is indicated in the long-term treatment of angina pectoris.  
**Heart Failure:** TOPROL-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, TOPROL-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

**CONTRAINDICATIONS**  
TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS) and in patients who are hypersensitive to any component of this product.

**WARNINGS**  
**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 TOPROL-XL, 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, TOPROL-XL 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 TOPROL-XL 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<sub>1</sub>-selectivity, however, TOPROL-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta<sub>1</sub>-selectivity is not absolute, a beta<sub>2</sub>-stimulating agent should be administered concomitantly, and the lowest possible dose of TOPROL-XL 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. TOPROL-XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, eg, 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:** TOPROL-XL 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.  
**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.

**PRECAUTIONS**  
**General:** TOPROL-XL 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. Worsening cardiac failure may occur during up-titration of TOPROL-XL. If such symptoms occur, diuretics should be increased and the dose of TOPROL-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of TOPROL-XL.  
**Information for Patients:** Patients should be advised to take TOPROL-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue TOPROL-XL 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 TOPROL-XL 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 TOPROL-XL. Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.  
**Laboratory Tests:** Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.  
**Drug Interactions:** Catecholamine-depleting drugs (eg, reserpine, monoamine 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 i.i.d. with immediate release metoprolol 50 mg i.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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three 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 (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 on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella/mammalian-microsome* mutagenicity test, and a nucleous aneuploidy test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella/mammalian-microsome* mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study 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.  
**Pregnancy Category C:** Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival 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. 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. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.  
**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. Caution should be exercised when TOPROL-XL is administered to a nursing woman.  
**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.  
**Geriatric Use:** Clinical studies of TOPROL-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients. Of the 1,990 patients with heart failure randomized to TOPROL-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug 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, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

**ADVERSE REACTIONS**  
**Hypertension and Angina:** 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 occurred in about 1 of 100 patients (see WARNINGS).  
**Gastrointestinal:** Diarrhea has been reported 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 TOPROL-XL.  
**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.  
**Heart Failure:** In the MERIT HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse events vs. 12.2% of placebo patients. The table below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

**Adverse Events Occurring in the MERIT-HF Study at an Incidence ≥1% in the TOPROL-XL Group and Greater Than Placebo by More Than 0.5%**

	TOPROL-XL N=1990 % of patients	Placebo N=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Other adverse events with an incidence of > 1% on TOPROL-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue.  
**Post-Marketing Experience:** The following adverse reactions have been reported with TOPROL-XL 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.

**OVERDOSAGE**  
**Acute Toxicity:** There have been a few reports of overdosage with TOPROL-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since TOPROL-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to TOPROL-XL. **Signs and Symptoms:** Overdosage of TOPROL-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis. **Treatment:** In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed: **Elimination of the Drug:** Gastric lavage should be performed. **Bradycardia:** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. **Hypotension:** A vasopressor should be administered, eg, levaterenol or dopamine. **Bronchospasm:** A beta<sub>2</sub>-stimulating agent and/or a theophylline derivative should be administered. **Cardiac Failure:** A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

**DOSAGE AND ADMINISTRATION**  
TOPROL-XL is an extended release tablet intended for once daily administration. For treatment of hypertension and angina, when switching from immediate release metoprolol to TOPROL-XL, the same total daily dose of TOPROL-XL should be used. Dosages of TOPROL-XL should be individualized and titration may be needed in some patients. TOPROL-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.  
**Hypertension:** The usual initial dosage is 25 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.  
**Angina Pectoris:** The dosage of TOPROL-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).  
**Heart Failure:** Dosage must be individualized and closely monitored during up-titration. Prior to initiation of TOPROL-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of TOPROL-XL is 25 mg once daily for two weeks in patients with NYHA class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of TOPROL-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. The dose of TOPROL-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce TOPROL-XL. If heart failure patients experience symptomatic bradycardia, the dose of TOPROL-XL should be reduced.

**HOW SUPPLIED**  
Tablets containing metoprolol succinate equivalent to the indicated weight of metoprolol tartrate, USP, are white, biconvex, film-coated, and scored.

Tablet	Shape	Engraving	Bottle of 100 NDC 0186-	Unit Dose Packages of 100 NDC 0186-
25 mg*	Oval	A B	1088-05	1088-39
50 mg	Round	A mo	1090-05	1090-39
100 mg	Round	A ms	1092-05	1092-39
200 mg	Oval	A my	1094-05	N/A

\*The 25-mg tablet is scored on both sides.  
Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.)

**NOTE:** This summary provides important information about TOPROL-XL. For more information, please ask your doctor or health care professional about the full Prescribing Information and discuss it with them.

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