



March 2009

UPDATE: TOPROL-XL[®] (metoprolol succinate) now generally available after AstraZeneca delivers significant supply across the US in response to generic shortage

Dear Doctor,

We are pleased to provide you with follow-up information to our letter of last month regarding the availability of TOPROL-XL.

As you know, after published reports^{i,ii} that two generic manufacturers had recalled or suspended their shipments of metoprolol succinate, AstraZeneca increased manufacturing of TOPROL-XL to help meet the US market demand.

Over the last number of weeks, AstraZeneca has delivered a significant quantity of TOPROL-XL to the US market in all strengths. Although outages at the retail pharmacy may still occur, we expect such circumstances to be increasingly rare, as wholesaler stocks have improved substantially.

AstraZeneca has been manufacturing TOPROL-XL for the US market since 1992 and has made significant investments to increase our capacity to address this unexpected change in the US market, while not adversely impacting supply available in the rest of the world.

Metoprolol succinate is a beta₁-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets.

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.

Metoprolol succinate is a once-a-day beta-blocker indicated for the following:

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.

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), and in patients who are hypersensitive to any component of this product.

Please see accompanying full Prescribing Information, including boxed WARNING regarding abrupt cessation of therapy, and the attached Important Safety Information about TOPROL-XL[®] (metoprolol succinate) extended-release tablets.

If you have any questions, or should you encounter difficulty in getting TOPROL-XL for your patients, please contact the AstraZeneca Information Center at 1-800-236-9933, between the hours of 8:00 am and 6:00 pm Eastern time, Monday through Friday.

Sincerely,

John McCarthy
Executive Director, Primary Care

James W. Hainer, MD, MPH
Sr. Director, Medical Science

Important Safety Information about TOPROL-XL[®] (metoprolol succinate) extended-release tablets

TOPROL-XL is indicated for the treatment of hypertension, alone or in combination with other antihypertensives; the long-term treatment of angina pectoris; and 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.

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

Patients taking TOPROL-XL should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. The dosage should be reduced gradually over a one-to-two-week period, and the patient should be carefully monitored.

TOPROL-XL should be used with caution in patients who have bronchospastic disease, diabetes, thyrotoxicosis, peripheral vascular disease, who are undergoing major surgery, or who take calcium channel blockers of the verapamil and diltiazem type.

There is a risk of worsening cardiac failure during up-titration of the dose of metoprolol succinate extended-release. Patients need to consult their physicians if they experience signs or symptoms of worsening heart failure such as weight gain or increased shortness of breath.

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

In clinical trials of patients with hypertension and angina pectoris the most common adverse events reported with immediate-release metoprolol tartrate are tiredness (10%), dizziness (10%), depression (5%), diarrhea (5%), pruritus or rash (5%), shortness of breath (3%), and bradycardia (3%).

In patients with heart failure, adverse events at an incidence $\geq 1\%$ in the group receiving TOPROL-XL extended-release and greater than placebo by more than 0.5% were dizziness/vertigo (1.8% vs 1.0%), bradycardia (1.5% vs 0.4%), and accident and or injury (1.4% vs 0.8%).

Please see accompanying full Prescribing Information.

TOPROL-XL is a registered trademark of the AstraZeneca group of companies.

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ⁱ Sandoz Recall, <http://www.fda.gov/bbs/topics/ENFORCE/2008/ENF01084.html>, accessed March 12, 2009

ⁱⁱ KV ceases shipping tablets, http://www.kvpharmaceutical.com/news_center_article.aspx?articleid=276, http://www.fda.gov/oc/po/firmrecalls/kv12_08.html accessed March 12, 2009.