

## METOTRUST XL-25/50

Metoprolol Succinate Extended-Release Tablets

### COMPOSITION

Each film-coated tablet of <b>Metotruster XL-25</b> contains:	
Metoprolol Succinate USP	23.75 mg
equivalent to Metoprolol Tartrate [as extended release form]	25 mg

Each film-coated tablet <b>Metotruster XL-50</b> contains:	
Metoprolol Succinate USP	47.50 mg
equivalent to Metoprolol Tartrate [as extended release form]	50 mg

### PHARMACOLOGY

#### Pharmacodynamics

**METOTRUST XL** has been formulated to provide a controlled and predictable release of metoprolol for once daily administration.

Metoprolol is a beta<sub>1</sub>-selective (cardioselective) adrenergic receptor blocking agent. At higher plasma concentrations however, metoprolol also inhibits beta<sub>2</sub>-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and the membrane-stabilizing activity is detectable at plasma concentrations much greater than that required for beta-blockade.

Studies indicate that metoprolol slows the sinus rate and decreases AV nodal conduction. Clinical pharmacology studies have also confirmed the beta-blocking activity of metoprolol in man, as shown by:

- (1) Reduction in heart rate and cardiac output at rest and upon exercise,
- (2) Reduction of systolic blood pressure upon exercise,
- (3) Inhibition of isoproterenol-induced tachycardia, and
- (4) Reduction of reflex orthostatic tachycardia.

The relative beta<sub>1</sub>-selectivity of metoprolol has been confirmed by the following:

- (1) In normal 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 doses.

Metoprolol extended-release administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total beta<sub>1</sub>-blockade over 24 hours in the dose range 100-400 mg. At a dosage of 50 mg once daily, metoprolol extended-release produced significantly higher total beta<sub>1</sub>-blockade over 24 hours than immediate release metoprolol. For metoprolol extended-release, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta<sub>1</sub>-blockade increased with increasing doses from 50 to 300 mg daily. In contrast to metoprolol extended-release, immediate release metoprolol given at a dose of 50-100 mg once a day produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with

metoprolol extended-release over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

A controlled cross-over study in heart failure patients compared the plasma concentrations and beta<sub>1</sub>-blocking effects of 50 mg immediate release metoprolol administered t.i.d., 100 mg and 200 mg metoprolol extended-release once daily. A 50 mg dose of immediate release metoprolol t.i.d. produced a peak plasma level of metoprolol similar to the peak level observed with 200 mg of metoprolol extended-release. A 200 mg dose of metoprolol extended-release produced a larger effect on suppression of exercise-induced heart rate over 24 hours compared to 50 mg t.i.d. of immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. The maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta<sub>1</sub>-blockade. Beta<sub>1</sub>-blocking effects correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative beta<sub>1</sub>-selectivity of metoprolol diminishes and blockade of beta<sub>2</sub>-adrenoceptors increases at plasma concentrations above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta<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.

In some studies, treatment with metoprolol extended-release produced an improvement in left ventricular ejection fraction. Metoprolol extended-release was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

**Hypertension:** Several possible mechanisms of the antihypertensive effects of beta-blocking agents 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.

**Angina Pectoris:** By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart, thus making it useful in the long-term management of angina pectoris.

**Heart Failure:** The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.

### **Pharmacokinetics**

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

Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta blocking activity. The systemic availability and half-life of metoprolol in patients with renal failure do not differ from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

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

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of metoprolol extended-release are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of metoprolol extended-release average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of metoprolol extended-release, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, beta<sub>1</sub>-blockade is comparable and dose-related.

The pharmacokinetic profile of metoprolol extended-release was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 mg to 200 mg once daily. The pharmacokinetics of metoprolol in pediatrics were similar to those described previously in adults. Metoprolol pharmacokinetics have not been investigated in patients less than 6 years of age.

## **INDICATIONS**

- Hypertension
- Angina pectoris
- Heart failure (NYHA class II or III)
- Migraine prophylaxis

## **DOSAGE & ADMINISTRATION**

### **Hypertension**

The usual initial dosage is 25 to 100 mg daily in a single dose. The dosage may be increased at weekly intervals until optimum blood pressure reduction is achieved. The maximum effect of any given dosage will be apparent after one week of therapy. Dosages above 400 mg per day have not been studied.

### **Angina Pectoris**

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.

### **Heart Failure**

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of **METOTRUST XL**, the dosing of diuretics, ACE inhibitors, and digitalis should be stabilized. The recommended starting dose 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 **METOTRUST 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 **METOTRUST XL** or temporarily discontinue it. The dose of **METOTRUST XL** should not be increased until symptoms of worsening heart failure have been stabilized. If heart failure patients experience symptomatic bradycardia, the dose of **METOTRUST XL** should be reduced.

### **Migraine prophylaxis**

The dosage is 100-200 mg once daily in the morning. In elderly patients, dose selection should be cautious, usually starting at the low end of the dosing range.

### **CONTRAINDICATIONS**

- Severe bradycardia
- Heart block greater than first degree
- Cardiogenic shock
- Decompensated cardiac failure
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Hypersensitivity to any component of this product

### **DRUG INTERACTIONS**

**Catecholamine-depleting drugs (e.g. reserpine, MAOIs)** may have an additive effect when given with beta-blocking agents. Patients should be carefully observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension, when these drugs are co-administered.

**Drugs inhibiting CYP2D6** such as quinidine, fluoxetine, paroxetine and propafenone are likely to increase metoprolol concentration. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

**Digitalis glycosides** & beta blockers, both slow atrioventricular conduction & decrease heart rate. Concomitant use can increase the risk of bradycardia.

**Clonidine:** Beta-blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs are co-administered, the betablocker 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 has been stopped.

**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.

### **WARNINGS & PRECAUTIONS**

#### **Discontinuation of therapy**

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 **METOTRUST XL**, particularly in patients with ischaemic 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, **METOTRUST XL** 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 **METOTRUST XL** therapy abruptly even in patients treated only for hypertension.

### **Bronchospastic diseases**

Patients with bronchospastic diseases should not receive beta blockers. Because of its relative beta<sub>1</sub> selectivity, **METOTRUST XL** may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. A beta<sub>2</sub>-stimulating agent should be administered concomitantly, and the lowest dose of **METOTRUST XL** should be used.

### **Major surgery**

The necessity of withdrawing beta-blocker 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 anaesthesia and surgical procedures.

### **Diabetes & Hypoglycemia**

**METOTRUST XL** should be used with caution in diabetic patients. 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 (e.g. 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.

### **Pheochromocytoma**

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

### **Cardiac Failure**

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

### **Hepatic Impairment**

Metoprolol should be used with caution in patients with impaired hepatic function.

### **Pregnancy**

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

### **Lactation**

Metoprolol is excreted in breast milk in small quantities. Caution should be exercised when **METOTRUST XL** is administered to a nursing woman.

### **Pediatric use**

Safety and effectiveness of **METOTRUST XL** have not been established in patients less than 6 years of age.

### **Geriatric use**

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.

### **UNDESIRABLE EFFECTS**

Most adverse effects have been mild and transient. Reported side effects include tiredness, dizziness, depression, headache, somnolence, insomnia, diarrhoea, pruritus, bradycardia, cold extremities, wheezing, dyspnea, nausea, dry mouth, constipation, flatulence and palpitations.

### **OVERDOSAGE**

Overdosage of **METOTRUST 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. 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, levarterenol or dopamine

*Bronchospasm:* a beta2-stimulating agent and/or a theophylline derivative should be administered

*Cardiac failure:* digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

### **PRESENTATION**

**METOTRUST XL-25** is available in strips of 10

**METOTRUST XL-50** is available in strips of 10