National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

METAP XL

2. QUALITY AND QUANTITATIVE COMPOSITION

Each film coated extended release tablet contains:

Metoprolol succinate USP 23.75 mg equivalent to Metoprolol succinate……25mg

Metoprolol succinate USP 47.5 mg equivalent to Metoprolol succinate……50mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

METAP XL 25mg: Yellow colored, circular, biconvex, film coated tablets with 'MICRO' engraved on both sides

METAP XL 50mg: White, circular, biconvex, film coated tablets with 'MICRO' engraved on both sides

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

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

Angina Pectoris

Metoprolol XL is indicated in the long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.

Heart Failure

Metoprolol 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, METOPROLOL XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

4.2 Posology and method of administration:

Hypertension

Adults: The usual initial dosage is 25 to 100 mg daily in a single dose. 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.

Pediatric Hypertensive Patients ≥ 6 Years of age: A pediatric clinical hypertension study in patients 6 to 16 years of age did not meet its primary endpoint (dose response for reduction in SBP); however, some other endpoints demonstrated effectiveness. If selected for treatment, the recommended starting dose of Metoprolol XL is 1 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily. Dosage should be adjusted according to blood pressure response. Doses above 2 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients.
Metoprolol XL is not recommended in pediatric patients < 6 years of age.

Angina Pectoris

Individualize the dosage of Metoprolol XL. The usual initial dosage is 100 mg daily, given in a single dose. Gradually increase the dosage 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, reduce the dosage gradually over a period of 1 - 2 weeks.

Heart Failure

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Metoprolol XL, stabilize the dose of other heart failure drug therapy. The recommended starting dose of Metoprolol 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. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of Metoprolol XL. Initial difficulty with titration should not preclude later attempts to introduce Metoprolol XL. If patients experience symptomatic bradycardia, reduce the dose of Metoprolol XL. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of Metoprolol XL or temporarily discontinuing it. The dose of Metoprolol XL should not be increased until symptoms of worsening heart failure have been stabilized.

4.3 Contraindications:

Metoprolol XL is contraindicated in severe bradycardia, second or third degree heart block, 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.

4.4 Special warning and precautions:

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 Metoprolol XL, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol XL, 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 abruptly discontinuing Metoprolol XL in patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol XL. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol XL. It may be necessary to lower the dose of Metoprolol XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol XL.

5.3 Bronchospastic Disease

Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta1 cardio-selectivity, however, Metoprolol XL may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of Metoprolol XL. Bronchodilators, including beta2-agonists, should be readily available or administered concomitantly.

5.4 Pheochromocytoma

If Metoprolol XL 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.

Major Surgery

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

Chronically administered beta-blocking therapy 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.

Diabetes and Hypoglycemia

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

Hepatic Impairment

Consider initiating Metoprolol XL therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

Thyrotoxicosis

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

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.

Peripheral Vascular Disease

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

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.

4.5 Interactions with Other Medicaments

Catecholamine Depleting Drugs

Catecholamine depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with Metoprolol XL plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP2D6 Inhibitors

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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/m2 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, use this drug during pregnancy only if clearly needed.

Lactation

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. Consider possible infant exposure when Metoprolol XL is administered to a nursing woman.

4.7 Effects on ability to drive and use machine:

As with all beta-blockers, metoprolol can affect patient's ability to drive and operate machinery. It should be taken into account that occasionally dizziness and fatigue may occur. Patient should be warned accordingly. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects:

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

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

Respiratory: Wheezing (bronchospasm), Dyspnea.

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

Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

Hypersensitive Reactions: Pruritus.

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.

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol 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, clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Laryngospasm, respiratory distress.

4.9 Overdose:

Signs and Symptoms - Over dosage of METOPROLOL XL may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, and bronchospasm, and hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment – Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Evaluate the need for atropine, adrenergic-stimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Heart failure and shock: May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α1 receptor agonistic drugs added in presence of vasodilation.

Bronchospasm: Can usually be reversed by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

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

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

Pharmacodynamics

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

Metoprolol is a beta1-selective (cardio selective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-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 beta1-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta2-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 FEV1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta1-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an Emax model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta1-blockade. Beta1-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma

concentrations from 30-540 nmol/L. The relative beta1-selectivity of metoprolol diminishes and blockade of beta2-adrenoceptors increases at plasma concentration 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. Beta2-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 other studies, treatment with METOPROLOL XL produced an improvement in left ventricular ejection fraction. METOPROLOL XL was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

5.2 Pharmacokinetic Properties:

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

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereo selective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate 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. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol cardio selectivity.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Metoprolol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of Metoprolol XL 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 XL, 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, β1-blockade is comparable and dose-related. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol XL administration.

Pediatrics: The pharmacokinetic profile of Metoprolol XL was studied in 120 pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol was similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

5.3 Preclinical safety Data:

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/m2 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/m2 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 nucleus anomaly 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/m2 basis, the daily dose of 200 mg in a 60-kg patient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

METAP XL 25mg:

Microcrystalline cellulose
Meth acrylic acid copolymer
Povidone
Hypromellose
Pregelatinised starch
Colloidal silicon dioxide
Talc
Steric acid
Titanium dioxide
Propylene glycol
Iron oxide yellow

METAP XL 50mg:

Microcrystalline cellulose
Meth acrylic acid copolymer
Povidone
Hypromellose
Pregelatinised starch
Colloidal silicon dioxide
Talc
Steric acid
Titanium dioxide
Propylene glycol

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store below 30°C. Keep away from the reach of children

6.5 Nature and contents of container:

Blister pack of 3 X 10 tablets

6.6 Special precautions for disposal

No special requirements

7. Marketing Authorization Holder:

MICRO LABS LIMITED
31, Race course road
Bangalore-560001
INDIA

8. Marketing Authorization Numbers

--

9. Date of first authorization

--

10. Date of revision of the text

Feb 2021