For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Biocon

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Metoprolol Succinate Prolonged-Release Tablets IP 25 mg / 50 mg

ACTIBLOK® IPR 25/50 एक्टीब्लौक आई पिआर २५/५०

This medication should be swallowed as a whole and not to be chewed or crushed. Do not suddenly stop taking this medication. Sharp chest pain, irregular heartbeat, and sometimes heart attack may occur if you suddenly stop Metoprolol Succinate Prolonged-Release Tablets. Tell your doctor if you have a history of diabetes or if you take medicine to lower your blood sugar. Metoprolol Succinate Prolonged-Release Tablets should not usually be used by patients who have a history of certain lung or breathing problems (eg, asthma) or who have a certain type of adrenal gland tumor (pheochromocytoma).

Composition:
ACTIBLOK® IPR 25
Each film-coated bilayered prolonged-release tablet contains:

Metoprolol Succinate IP	23.75 mg
equivalent to Metoprolol Tartrate	25 mg
Excipients	q.s.

Colour: Sunset Yellow

ACTIBLOK® IPR 50
Each film-coated bilayered prolonged-release tablet contains:

Metoprolol Succinate IP	47.5 mg
equivalent to Metoprolol Tartrate	50 mg
Excipients	q.s.

Colour: Brilliant Blue

PHARMACEUTICAL FORM: Tablets

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic Group: Beta blocking agents, selective
ATC code: C07AB02

Description:
Metoprolol succinate prolonged-release tablet
A beta1-selective (cardioselective) adrenoceptor blocker for oral administration. The tablets contain Metoprolol succinate equivalent to 25 mg and 50 mg of Metoprolol Tartrate respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Molecular Formula: $(C_{15}H_{25}NO_3)_2 \bullet C_4H_6O_4$ Molecular Weight: 652.81

PHARMACOLOGICAL PROPERTIES:
Mechanism of action:
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.

Pharmacokinetic Properties:
Absorption:
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. In comparison to conventional Metoprolol, the plasma Metoprolol levels following administration of Metoprolol succinate prolonged-release tablets are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. At steady state the average bioavailability of Metoprolol following administration of Metoprolol succinate prolonged-release tablets, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional Metoprolol. The bioavailability of Metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol succinate prolonged-release tablets administration.

Distribution:
Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Metabolism:
Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. 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.

Elimination:
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.

CLINICAL PARTICULARS
Therapeutic Indication:
- ACTIBLOK® IPR 25 /50 are indicated for the treatment of hypertension
- ACTIBLOK® IPR 25 /50 are indicated in the long-term treatment of angina pectoris

Posology and Method of Administration:
Metoprolol succinate prolonged-release tablet is intended for once daily administration. For treatment of hypertension and angina, when switching from immediate-release metoprolol to metoprolol succinate prolonged release tablet, use the same total daily dose of metoprolol immediate release. Individualize the dosage of metoprolol succinate prolonged-release tablet. Titration may be needed in some patients.

Hypertention
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 succinate prolonged-release tablet is 1.0 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 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients

Angina Pectoris
Individualize the dosage of Metoprolol succinate prolonged-release tablet. 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 succinate prolonged-release tablet, stabilize the dose of other heart failure drug therapy. The recommended starting dose of metoprolol succinate prolonged-release tablet 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 succinate prolonged-release tablet. Initial difficulty with titration should not preclude later attempts to introduce metoprolol succinate prolonged-release tablet. If patients experience symptomatic bradycardia, reduce the dose of metoprolol succinate prolonged-release tablet. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of metoprolol succinate prolonged-release tablet or temporarily discontinuing it. The dose of metoprolol succinate prolonged-release tablet should not be increased until symptoms of worsening heart failure have been stabilized.

Contraindication:
Metoprolol succinate prolonged release tablets is contraindicated in patients who are hypersensitive to any components of this product, and also in bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place).

Special Warnings and Precautions for Use
Bronchospastic Diseases:
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta1-cardio selectivity, however, Metoprolol succinate prolonged-release tablets may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta1-selectivity is not absolute, a beta 2-stimulating agent should be administered concomitantly, and the lowest possible dose of Metoprolol succinate prolonged-release tablets should be used.

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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.

Metoprolol succinate prolonged-release tablets, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., 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:
Metoprolol succinate prolonged-release tablets should be used with caution in patients with diabetes 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 (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 in such individuals.

PRECAUTIONS:
General:
Metoprolol succinate prolonged-release tablets 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.

Laboratory tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Adverse reactions:
Central Nervous System
Headache, nightmares, insomnia Tiredness, dizziness, Depression, and Mental confusion have occurred.

Cardiovascular
Shortness of breath, bradycardia, Cold extremities, palpitations, congestive heart failure, peripheral edema, and hypotension have occurred.
Respiratory
Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients.
Gastrointestinal
Diarrhea, Nausea, Dry mouth, Gastric pain, Constipation, Flatulence, and Heartburn have been reported in about 1 of 100 patients. Post-marketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hypersensitive Reactions
Pruritus or rash, 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, 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.

Special Populations:
Renal insufficiency:
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 dosage is usually needed in patients with chronic renal failure.

Liver impairment:
Metoprolol succinate prolonged-release tablets should be used with caution in patients with impaired hepatic function.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric use
Clinical studies of Metoprolol succinate prolonged-release tablets in hypertension did not include sufficient numbers of subjects aged 65 years 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.

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.

OVERDOSAGE:
There is no specific antidote.
If any over dose is suspected, gastric lavage should be performed to prevent the further absorption of the drug. Atropine is administered to counteract the bradycardia. If there is no response to vagal blockade, isoproterenol is administered under caution. Vasopressor like dopamine is given in case of severe hypotension.

Bronchospasm: A beta 2 agonist and or theophylline derivative should be given.

Presentation:
ACTIBLOK® IPR 25/50 available in blister pack of 10 tablets each.

Storage:Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

Shelf life: Refer carton/blister.

Special Precautions for Disposal and Other Handling
Any unused medicinal product should be disposed off in accordance with the local requirements.
The tablet should be swallowed as a whole and not to be crushed or chewed.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

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