Biocon

℞

Amlodipine + Metoprolol (ER) Tabelts

ACTIBLOK® AM 25/50 LYOïosÉÉM L LqÉ 25/50

COMPOSITION
ACTIBLOK AM® 25
Each film coated tablet contains:
Amlodipine Besilate IP
Equivalent to Amlodipine 5 mg
Metoprolol Succinate USP 23.75 mg
Equivalent to Metoprolol Tartrate 25 mg
(as extended release form)
Colours: Ponceau 4R & Titanium Dioxide IP

ACTIBLOK AM® 50
Each film coated tablet contains:
Amlodipine Besilate IP
Equivalent to Amlodipine 5 mg
Metoprolol Succinate USP 47.5 mg
Equivalent to Metoprolol Tartrate 50 mg
(as extended release form)
Colours: Sunset Yellow & Titanium Dioxide IP

PHARMACEUTICAL FORM
Film coated tablets

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Metoprolol and other antihypertensives
ATC Code: C07FB02

Amlodipine
Amlodipine besilate is the besilate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besilate is chemically 3-Ethyl-5-methyl (±)-2-[(2aminoethoxy)methyl]-4- (2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate mono benzenesulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$. Amlodipine besilate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol.

Metoprolol succinate as extended-release form (Metoprolol ER)
Metoprolol is a beta$_1$-selective (cardioselective) adrenoceptor blocker for oral administration. Its chemical name is (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Molecular formula is $(C_{15}H_{25}NO_3)_2 C_4H_6O_4$ and molecular weight is 652.81.

Metoprolol succinate is a white crystalline powder. It is freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl acetate, acetone, diethylether and heptane.

Mechanism of Action
Amlodipine/Metoprolol ER
Amlodipine is a dihydropyridine calcium channel blocker and metoprolol is a beta$_1$ (β_1)-selective (cardioselective) adrenergic receptor blocking agent. Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle (more selective) and cardiac muscle and there by inhibits their contractile process (serum calcium concentration is not affected). It is also a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure by which relieves angina (exertional and vasospastic). Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for β-blockade.

Pharmacokinetic Properties
Absorption:
After oral administration of amlodipine, a peak plasma concentration is achieved between 6 to 12 hours and absolute bioavailability has been estimated between 64% to 90%. The plasma levels of conventional metoprolol is 50%, (indicates first pass metabolism) to that of its intravenous administration. The plasma levels of metoprolol following administration of metoprolol ER is characterized by lower peaks, longer time to peak and significantly lower peak to trough variation and at steady state, the average bioavailability of metoprolol across the dosage range of 50 to 400 mg once daily, was 77% relative to conventional metoprolol in its corresponding single or divided doses . The bioavailability of metoprolol ER (in case of increased dose to 400 mg once daily) and amlodipine is not altered by the presence of food.

Distribution and Metabolism:
Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine whereas, metoprolol is primarily metabolized by CYP2D6 and exhibits stereoselective metabolism that is dependent on oxidation phenotype. Concomitant use of CYP2D6 inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardioselectivity (see section Drug Interactions). 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.

Elimination:
Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours and its steady-state plasma levels are reached after 7 to 8 days of consecutive daily dosing. The plasma half-life of metoprolol ranges from 3 to 7 hours and less than 5% of an oral dose of metoprolol is recovered unchanged in the urine.

Special Population
Renal insufficiency:
The pharmacokinetics of amlodipine/metoprolol ER is not significantly influenced by renal impairment. Patients with renal failure may therefore can take the usual initial dose (see section Posology and Method of Administration).

Geriatric and Hepatic insufficiency:
Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. Whereas, in general, for metoprolol, 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 (see section Posology and Method of Administration).

Pediatric use:
The pharmacokinetic profile of amlodipine (1.25 mg to 20 mg) and metoprolol ER (12.5 mg to 200 mg) once daily, studied in pediatric hypertensive patients (6 to 17 years of age) was similar to adults. Age, gender, race, and ideal body weight had no significant effect. Amlodipine and metoprolol pharmacokinetics have not been investigated in patients < 6 years of age (see section Posology and Method of Administration).

Preclinical Safety Data
Carcinogenicity
Rats and mice, treated with amlodipine maleate (at dosage levels of 0.5, 1.25, and 2.5 mg/kg/day) and rats treated with metoprolol tartarate (at 3 oral dosage levels of up to 800 mg/kg/day ,41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60 kg patient) in the diet for up to 2 years, showed no evidence of a carcinogenic effect, inspite of some histological changes like increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia.

A 21 month study in Swiss albino mice treated with metoprolol at 3 oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60 kg patient), showed benign lung tumors (small adenomas) more frequently in female mice which received the highest dose compared to untreated control animals. Whereas, the same 21 month study which was repeated in CD-1 mice showed no statistically or biologically significant differences between treated and control mice of either sex for any type of tumor.

Genotoxicity and Mutagenicity
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 and no drug related mutagenicity and was detected due to amlodipine at either the gene or chromosome level.

Fertility
There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day# (8 times the maximum recommended human dose of 10 mg/day on mg/m^2 basis) and on rats treated with metoprolol (at doses up to 22 times, on mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient)
#based on patient weight of 50 kg.

CLINICAL PARTICULARS
Therapeutic Indications
- Hypertension
- Angina pectoris
- Symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin
- Chronic Artery Diseases (CAD)
  - Chronic stable angina
  - Vasospastic angina (Prinzmetal's or Variant Angina)
  - Angiographically documented CAD

Posology and Method of Administration
Adults:
Individualize the dosage of amlodipine and metoprolol ER. The usual initial antihypertensive dose range of amlodipine and metoprolol ER is 5 mg to 10 mg and 25 mg to 100 mg respectively once daily. For angina, the single oral dose of metoprolol ER is 100 mg daily. The metoprolol dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction (for hypertension) and pronounced slowing of heart rate (for angina) is achieved. Dosages above 400 mg of metoprolol per day have not been studied. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy, so titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level.

Geriatric and Hepatic Impairment:
Amlodipine, when given in combination with other anti-hypertensive therapy or to the small, fragile, elderly patients and patients with hepatic insufficiency may be started on 2.5 mg once daily. For metoprolol ER, dose selection should be cautious (see section Pharmacokinetic Properties).

Pediatrics:
The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6 to 17 years is 2.5 mg to 5 mg once daily. Though, metoprolol ER failed to reduce systolic blood pressure, SBP (primary end point) in a pediatric study, it demonstrated its effectiveness in other endpoints. If metoprolol ER is selected for treatment, the recommended starting dose of is 1.0 mg/kg once daily, with maximum initial dose not exceeding 50 mg once daily. Dosage should be adjusted according to blood pressure response. Doses in excess of 5 mg and 200 mg of amlodipine and metoprolol ER respectively, once daily, have not been studied in pediatric patients. Amlodipine and metoprolol ER is not recommended in pediatric patients < 6 years of age (see section Special Warnings and Precautions for Use).

Heart Failure:
Dosage of metoprolol ER must be individualized and closely monitored during up-titration. Prior to initiation of metoprolol ER, stabilize the dose of other heart failure drug therapy. The recommended starting dose of metoprolol ER is 25 mg once daily for 2 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 2 weeks to the highest dosage level tolerated by the patient or up to 200 mg of metoprolol ER. If patients experience symptomatic bradycardia, reduce the dose of metoprolol ER. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of metoprolol ER or temporarily discontinuing it. The dose of metoprolol ER should not be increased until symptoms of worsening heart failure have been stabilized.

Contraindications
Amlodipine and metoprolol ER tablets are contraindicated in patients who are hypersensitive to any component 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
Hypotension:
Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina and/or Myocardial Infarction:
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine besylate, particularly in patients with severe obstructive coronary artery disease.

Beta-Blocker Withdrawal:
Amlodipine is not a β-blocker and therefore gives no protection against the dangers of abrupt β-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of β-blocker.

Patients with Hepatic Failure:
Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering amlodipine to patients with severe hepatic impairment (see section Posology and Method of Administration).

Hepatic Impairment:
Consider initiating metoprolol ER therapy at doses lower than those recommended for a given indication. Gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

Pheochromocytoma:
An alpha (α)-blocking agent should be initiated prior to the use of any β-blocking agent.

Bronchospastic Diseases:
Patients with bronchospastic diseases should not receive **β**-blockers, because of its relative β_1-selectivity. However, metoprolol ER may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. A β_2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol ER should be used.

Major Surgery:
Avoid initiation of a high-dose regimen of metoprolol ER 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 β-blocking therapy should not be routinely withdrawn prior to major surgery, because 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:
Metoprolol ER should be used with caution in diabetic patients, if a β-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 β-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.

Biocon

℞

Amlodipine + Metoprolol (ER) Tabelts

ACTIBLOK® AM 25/50 LYOÏosÉÉM L LqÉ 25/50

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

Drug Interactions
Amlodipine
The effect of and on following drugs when co-administered with amlodipine

Drug class/drugs	Comments
Cimetidine, grapefruit Juice, magnesium and aluminum hydroxide antacid, sildenafil, atorvastatin,digoxin,ethanol, erythromycin, warfarin	➢ No effect on the pharmacokinetics
Simvastatin	➢ Increased the exposure of the drug
Diltiazem, ketoconazole, itraconazole, ritonavir	➢ Increased amlodipine systemic exposure

Metoprolol ER
The effect of and on following drugs when co –administered with metoprolol ER

Drug/drug class	Comments
Catecholamine Depleting Drugs: Reserpine, monoamine oxidase (MAO) inhibitors	➢ Additive effect when given with beta-blocking agents ➢ Hypotension or marked bradycardia, vertigo, syncope, or postural hypotension.
CYP2D6 Inhibitors Quinidine, fluoxetine, paroxetine and propafenone	➢ Increase metoprolol concentration ➢ Decrease the cardioselectivity of metoprolol.
Digitalis, Clonidine, and Calcium Channel Blockers (diltiazem and verapamil)	➢ Risk of bradycardia. ➢ Withdraw the beta-blocker several days before the gradual withdrawal of clonidine because, β-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.

Pregnancy and Lactation
Pregnancy Category C:
No evidence of teratogenicity or other embryo/fetal toxicity was found in rats (treated with metoprolol tartarate at doses up to 22 times, on mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient) and in pregnant rats and rabbits (treated with amlodipine maleate at doses up to 10 mg amlodipine/kg/day, 8 times* and 23 times* respectively ,the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, increased post-implantation, decreased neonatal survival, prolonged gestation period, increased duration of labor, in case of metoprolol and litter size reduction (about 50%),increase in intrauterine deaths in rats in case of amlodipine was observed. There are no adequate and well-controlled studies of amlodipine and metoprolol in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug combination during pregnancy only if clearly needed.
*Based on patient weight of 50 kg.

Lactation:
Metoprolol is known to be excreted in milk in very small quantities, whereas it is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine and metoprolol is administered.

Effects on Ability to Drive and Use Machines
Amlodipine and metoprolol may affect the ability to drive and operate machinery. Patients should be warned accordingly. These effects may possibly be enhanced in case of concomitant ingestion of alcohol or after changing to another medicinal product.

Undesirable Effects
Amlodipine
Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity.

Common side effects ➢ Headache, edema dizziness, flushing and palpitation.	
Adverse Effects >1.0% ➢ Fatigue, nausea, abdominal pain and somnolence	
Adverse Effects <1% but >0.1%	
General	➢ Allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Cardiovascular	➢ Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.
Central and Peripheral Nervous System	➢ Hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.
Gastrointestinal	➢ Anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
Musculoskeletal System *Psychiatric*	➢ Arthralgia, arthrosis, muscle cramps, myalgia, sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System	➢ Dyspnea, epistaxis.
Skin and Appendages	➢ Angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.
Special Senses	➢ Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System	➢ Micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System	➢ Dry mouth, sweating increased
Metabolic and Nutritional	➢ Hyperglycemia, thirst.
Hemopoietic	➢ Leukopenia, purpura, thrombocytopenia
Adverse Effects <0.1% ➢ Cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation and xerophthalmia.	
Postmarketing Experience ➢ Gynecomastia, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis.	

Metoprolol ER

Adverse Reactions (>2%) ➢ Tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash.	
Adverse Reactions (>1%) ➢ Dizziness, vertigo, bradycardia, accident/or injury.	
Post-operative Adverse Events ➢ Bradycardia, hypotension, stroke	
Post-Marketing Experience	
Central Nervous System	➢ Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia. anxiety/nervousness, hallucinations, paresthesia.
Cardiovascular	➢ Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension
Respiratory	➢ Wheezing (bronchospasm) and dyspnea.
Gastrointestinal	➢ Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting. Very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations
Hypersensitive Reactions	➢ Pruritus or rash, worsening of psoriasis
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 [Adverse reactions reported with other β-adrenergic blocking agents (not listed above)]	
Central Nervous System	➢ Reversible mental depression progressing to catatonia, 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.
Laboratory Test Findings ➢ Elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.	

Overdose
Amlodipine
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Metoprolol ER
There is no specific antidote. 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.

Bradycardia:
Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

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

Bronchospasm:
Administer a β_2-agonist, including albuterol inhalation, or an oral theophylline derivative.

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.

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

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable

Shelf Life
24 months

Storage and Precautions
Store in cool, dry place
Keep out of reach of children

Special Precautions for Disposal and Other Handling
Tablet to be swallowed as whole and not to be chewed or crushed.

Nature and Contents of Container
Each pack consists 10 tablets in a blister; such 10 blisters in carton, along with pack insert

MANUFACTURED BY
WINDLAS Biotech Limited
40/1, Mohabewala Industrial Area, SBI Road, Dehradun – 248 110

MARKETED BY
BIOCON Limited,
20th KM, Hosur Road, Electronics City, Bangalore 560100

® - Registered trademark of Biocon Limited

For further details, please contact:
Medical Advisor
20th KM, Hosur Road, Electronics City, Bangalore 560100

Leaflet revised August 2012

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

BF/LL/10201/01