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

℞ Cilnidipine, Telmisartan & Metoprolol Succinate (ER) Tablets

CILACAR®-TM 25/50

WARNING: AVOID USE IN PREGNANCY, ISCHEMIC HEART DISEASE

When pregnancy is detected, discontinue tablets as soon as possible. Drugs that act directly on the renin-angiotensin system like Telmisartan can cause injury and even death to the developing foetus.

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 Succinate Extended-Release Tablet, 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, Metoprolol succinate extended release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients 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 Metoprolol succinate extended release tablet therapy abruptly even in patients treated only for hypertension.

COMPOSITION

Cilnidipine, Telmisartan & Metoprolol Succinate (ER) Tablets
CILACAR®-TM 25
Each film coated tablet contains:
Metoprolol Succinate IP .... 23.75 mg
Eq. to Metoprolol Tartrate .... 25 mg
(As Extended Release)
Cilnidipine IP .... 10 mg
Telmisartan IP .... 40 mg
Excipients .... q.s.
Colours: Ferric Oxide USPNF Yellow & Titanium Dioxide IP

Cilnidipine, Telmisartan & Metoprolol Succinate (ER) Tablets
CILACAR®-TM 50
Each film coated tablet contains:
Metoprolol Succinate IP .... 47.5 mg
Eq. to Metoprolol Tartrate .... 50 mg
(As Extended Release)
Cilnidipine IP .... 10 mg
Telmisartan IP .... 40 mg
Excipients .... q.s.
Colours: Ferric Oxide USPNF Red & Titanium Dioxide IP

PHARMACEUTICAL FORM

Film Coated Tablet

THERAPEUTIC INDICATION

It is indicated for the treatment of patients with uncontrolled essential hypertension and stable ischemic heart disease.

DOSAGE AND ADMINISTRATION

Posology

The recommended oral dosage is 1 tablet once daily or as directed by the Physician.
Dosage must be individualized.
Method of administration: For oral use only.
The patient should be instructed to swallow tablet as whole with liquid and must not be chewed or crushed. To achieve the best possible results, take your dose at the same time(s) each day.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to any of the active substance(s) or any other component of this formulation.
• Metoprolol is contraindicated in patients with: Hypotension, sinus bradycardia, second or third degree heart block, cardiogenic shock, severe peripheral arterial circulatory disorders, sick-sinus syndrome, untreated pheochromocytoma, overt cardiac failure, bradycardia (< 45 beats/minute), continuous or intermittent inotropic therapy acting through beta-receptor agonism, metabolic acidosis, decompensated cardiac failure (pulmonary edema, hypoperfusion or hypotension), uncontrolled heart failure, severe asthma or history of severe bronchospasm and hypersensitivity to metoprolol, other beta-blockers (cross sensitivity between beta-blockers can occur) and related derivatives.
Metoprolol is also contraindicated in acute myocardial infarction patients with a heart rate <45 beats/minute; second- and third-degree heart block; significant first-degree heart block (P-R interval > 0.24 sec); systolic blood pressure < 100 mm Hg; or moderate-to-severe cardiac failure.
• Cilnidipine is contraindicated in: Shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis), unstable angina (excluding Prinzmetal's angina), and severe hypotension, haemodynamically unstable heart failure after acute myocardial infarction.
• Telmisartan is contraindicated in:
- Second and third trimester of pregnancy.
- Biliary obstructive disorders.
- Severe hepatic impairment.
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warning: Fetal Toxicity

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. When pregnancy is detected, this product should be discontinued as soon as possible.

Metoprolol

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 succinate extended-release tablets, 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, metoprolol succinate extended-release tablet 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 metoprolol succinate extended-release tablet therapy abruptly even in patients treated only for hypertension.
Bronchospastic Diseases
Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta1-selectivity, however, metoprolol succinate extended-release tablet 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 beta2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol succinate extended- release tablets should be used.
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 extended-release tablet, 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 extended-release tablets should be used with caution in diabetic patients 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.
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.
General
Metoprolol succinate extended-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.
Worsening cardiac failure may occur during up-titration of metoprolol succinate extended-release tablets. If such symptoms occur, diuretics should be increased and the dose of metoprolol succinate extended-release tablets should not be advanced until clinical stability is restored. It may be necessary to lower the dose of metoprolol succinate extended release tablet or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of metoprolol succinate extended-release tablets.
Information for Patients
Patients should be advised to take metoprolol succinate extended-release tablets regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue metoprolol succinate extended-release tablets without consulting the physician.
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with metoprolol succinate extended release tablets has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking metoprolol succinate extended-release tablets.
Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Cilnidipine

It is advisable for elderly patients to initiate therapy with small doses, and gradually decrease dose with careful symptom observation when drug withdrawing. Other drug is recommended when daily dose is decreased to 5mg. Drug withdraw should be directed by the physician. Hypotension, poor cardiac reserve, and heart failure. Sudden withdrawal may exacerbate angina. Discontinue in patients who experience ischemic pain following administration. Caution should be exercised during Cilnidipine use in pregnancy and lactation.

Telmisartan

Pregnancy: Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
Hepatic impairment: Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.
Renovascular hypertension: There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.
Renal impairment and kidney transplantation: When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation.
Intravascular hypovolaemia: Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS): There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.
Other conditions with stimulation of the renin-angiotensin-aldosterone system: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.
Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
Diabetic patients treated with insulin or antidiabetics: In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.
Hyperkalaemia: The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.
Close-monitoring of serum potassium in at risk patients is recommended.
Ethnic differences: As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.
Other: As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

The Product Cilacar TM 25 is an extended-release tablet. The Metroprolol Tartrate part is an extended release from which the drug is released slowly at a predetermined rate in order to maintain a drug concentration for a specific period of time through a matrix. Sometimes the tablet being noticed in excreta is a 'Ghost Tablet" which is only the outer shell of a pill without active ingredients. When this happens a person may worry the medication did not dissolve and did not work. Finding a pill in the stool is entirely normal for long-acting medications.

DRUG INTERACTIONS

Metoprolol

Catecholamine-depleting drugs (e.g, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol succinate extended-release tablets plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
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, co-administration 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, co-administration 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 cardioselectivity of metoprolol.
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta blocker 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 administration has stopped.

Cilnidipine

Cilnidipine can interact with other antihypertensives; aldesleukin; antipsychotics that cause hypotension; may modify insulin and glucose responses; quinidine; carbamazepine; phenytoin; rifampicin; cimetidine; erythromycin and anti-psychotic drugs.

Telmisartan

Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.
As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).
The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.
Concomitant use not recommended
Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Concomitant use requiring caution
Non-steroidal anti-inflammatory medicinal products
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.
In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.
Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.
To be taken into account with concomitant use
Other antihypertensive agents
The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.
Corticosteroids (systemic use)
Reduction of the antihypertensive effect.

USE IN SPECIFIC POPULATIONS

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.
Metoprolol: Pregnancy category C. Upon confirming the diagnosis of pregnancy, women should immediately inform the doctor. Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 11 times the maximum daily human dose of 450 mg, when based on surface area. There are no adequate and well-controlled studies in pregnant women. The amount of data on the use of metoprolol inn pregnant women is limited. The risk to the fetus/mother is unknown. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Caution should be exercised during Cilnidipine use in pregnancy.
Telmisartan: Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). There are no adequate data from the use of Telmisartan in pregnant women. Studies in animals have shown reproductive toxicity.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

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.
It is not known whether cilnidipine is distributed in human breast milk or not However, caution should be exercised during cilnidipine use in lactation.
Because no information is available regarding the use of Telmisartan during breast-feeding, Telmisartan is not recommended and alternative treatments with better established safety profiles during breast feeding are preferable, especially while nursing a newborn or preterm infant.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical trials of metoprolol in hypertension did not include sufficient numbers of elderly patients to determine whether patients over 65 years of age differ from younger subjects in their response to metoprolol. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from younger patients.
Of the total number of patients receiving telmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment of telmisartan is necessary for elderly patients.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan.
There's no report of cilnidipine's effect on the ability to drive and use machines. However, cilnidipine can have minor or moderate influence on the ability to drive and use machines. If patients taking cilnidipine suffer from dizziness, headache or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.
As with all beta-blockers, metoprolol may affect patients' ability to drive and operate machinery. It should be taken into account that occasionally dizziness or fatigue may occur. 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

Metoprolol

The following are the adverse reactions: Worsening angina or myocardial infarction, worsening heart failure, and worsening AV block.
Clinical Trials Experience:
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.
Hypertension and Angina: Most adverse reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia and rash.
Post-marketing experience:
The following adverse reactions have been identified during post-approval use of metoprolol extended-release 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.
Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.
Respiratory: Wheezing (bronchospasm), dyspnea.
Gastrointestinal: Nausea, dry mouth, constipations, flatulence, heartburn, hepatitis, vomiting.
Hypersensitive Reactions: pruritis.
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 extended-release.
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.
Laboratory Test Findings: Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase and lactate dehydrogenase.

Cilnidipine

Dizziness; flushing; headache; hypotension; peripheral oedema; tachycardia; palpitations; GI disturbances; increased micturition frequency; lethargy; eye pain; depression; ischaemic chest pain; cerebral or myocardial ischaemia; transient blindness; rashes; fever; abnormal liver function; gingival hyperplasia; myalgia; tremor; impotence.
The mostly reported adverse reactions (mild and rare adverse reactions) during cilnidipine treatment are nausea, headaches, swelling, low blood pressure, and edema (water retention), dizziness, cardiopalmus, and puffiness, which can be tolerated by most patients, and no management should be taken.
Lab Interference: Falsely elevated spectrophotometric values of urinary vanillylmandelic acid.

Telmisartan

Summary of the safety profile
Serious adverse reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.
The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4% vs 43.9%) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.
Adverse reactions have been ranked under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 1/10,000)
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Infections and infestations
Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
Rare: Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders
Uncommon: Anaemia
Rare: Eosinophilia, thrombocytopenia
Immune system disorders
Rare: Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders
Uncommon: Hyperkalaemia
Rare: Hypoglycaemia (in diabetic patients)
Psychiatric disorders
Uncommon: Depression, insomnia
Rare: Anxiety
Nervous system disorders
Uncommon: Syncope
Rare: Somnolence
Eye disorders
Rare: Visual disturbance
Ear and labyrinth disorders
Uncommon: Vertigo
Cardiac disorders
Uncommon: Bradycardia
Rare: Tachycardia
Vascular disorders
Uncommon: Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough
Very rare: Interstitial lung disease[3]
Gastrointestinal disorders
Uncommon: Abdominal pain, diarrhoea, dyspepsia , flatulence, vomiting
Rare: Stomach discomfort, dry mouth, dysgeusia
Hepato-biliary disorders
Rare: Hepatic function abnormal/liver disorder[4]
Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis, pruritus, rash
Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders
Uncommon: Myalgia, back pain (e.g. sciatica), muscle spasms
Rare: Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)
Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure
General disorders and administration site conditions
Uncommon: Chest pain, asthenia (weakness)
Rare: Influenza-like illness
Investigations
Uncommon: Blood creatinine increased
Rare: Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased
1,2,3,4: for further descriptions, please see sub-section *"Description of selected adverse reactions"*
Description of selected adverse reactions
[1]Sepsis
In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.
[2]Hypotension
This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.
[3]Interstitial lung disease
Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.
[4]Hepatic function abnormal / liver disorder
Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com.

OVERDOSE

Metoprolol

Overdosage of metoprolol extended-release may lead to severe bradycardia, hypotension and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.
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.

Cilnidipine

The general symptoms of overdose with cilnidipine are: hypotension and low heartbeat, or coma. Immediately contact your nearby emergency department before these symptoms get worse. Appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken.

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Metoprolol
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 atrioventricular (AV) nodal conduction. Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in the 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.
Cilnidipine
Cilnidipine is a dihydropyridine calcium antagonist. Compared with other calcium antagonists, cilnidipine can act on the N-type calcium channel that existing sympathetic nerve end besides acting on L-type calcium channel that similar to most of the calcium antagonists. It acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of norepinephrine and suppressing the increase in stress blood pressure. It can be combined with the fluazifop sites in L-type calcium channel on vascular smooth muscle cellular membrane, and inhibit the across membrane inflow of Ca2+ through L-type calcium channel, accordingly relax and expand vascular smooth muscles to reduce blood pressure.
Telmisartan
Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterized AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse events. In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Pharmacokinetic properties

Metoprolol
Absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following IV administration, indicating about 50% first-pass metabolism. The plasma metoprolol levels following administration of metoprolol succinate extended-release 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 extended-release, across the dosage range of 50-400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Metoprolol crosses the blood brain barrier and has been reported in the cerebral spinal fluid (CSF) at a concentration measuring 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 when administered orally, it exhibits a stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3-7 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.
Cilnidipine
Cilnidipine presents a very rapid absorption with a maximum peaked concentration after 2 hours. Its distribution tends to be higher in the liver as well as in kidneys, plasma and other tissues. Cilnidipine does not present a high accumulation in the tissue after repeated oral administration. Drugs on the group of dihydropyridines such as cilnidipine tend to have a large volume of distribution. Cilnidipine presents a very high protein binding that represents to even 98% of the administered dose. Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by a dehydrogenation process. The major enzymatic isoform involved in cilnidipine dehydrogenation of the dihydropyridine ring is CYP3A. Cilnidipine gets eliminated through the urine in a proportion of 20% of the administered dose and 80% is eliminated by the feces. The half-life of the hypotensive effect for cilnidipine is of about 20.4 min.
Telmisartan
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 L. Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (Cmax) and to a smaller extent, the AUC; increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).
Linearity/non-linearity: The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. Cmax and to a lesser extent AUC increase disproportionately at doses above 40 mg.

INCOMPATIBILITY

None stated.

STORAGE INSTRUCTIONS

Store at a temperature not exceeding 30ºC.
Keep out of reach of children.

Important: Moisture sensitive tablets - Do not remove from strip until immediately before administration.

PACKAGING INFORMATION

Blister of 2 tablets and 10 tablets.

Marketed by & ® Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.
Note: This prescribing information is applicable for India Market only.

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