TELEXA®- M 25

PRODUCT DESCRIPTION:

TELEXA®-M 25 Tablets:

Each tablet contains,
Telmisartan – 40 mg
Metoprolol Succinate – 25 mg (as Extended release)

Rx only
Prescribing Information

USE IN PREGNANCY

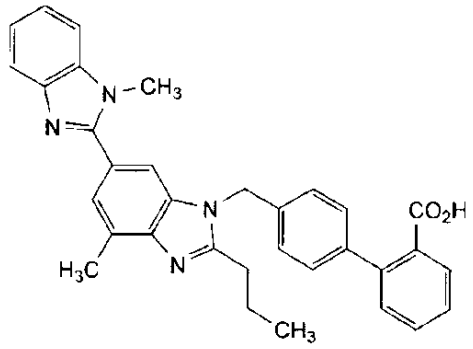
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

When pregnancy is detected, TELEXA®- M 25 tablets should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality**

PHARMACEUTICAL DESCRIPTION:

Telmisartan:

Structural formula:



Molecular formula: $C_{33}H_{30}N_4O_2$

Chemical name:
4'-[[4-Methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl] methyl] bi phenyl-2-carboxylic acid

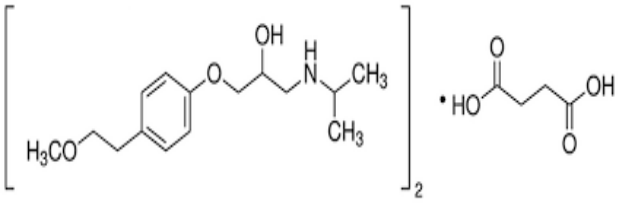
Molecular weight: 514.6 g/mol

pKa: 4.45

Telmisartan is a specific non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan is a white or slightly yellowish crystalline powder. It is practically insoluble in water, slightly soluble in methanol and sparingly soluble in methylene chloride.

Metoprolol Succinate:

Structural formula:



Molecular formula: $C_{34}H_{56}N_2O_{10}$

Chemical name: Di-(±)-1-(isopropylamine)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol succinate

Molecular weight: 652.80 g/mol

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, and practically insoluble in ethyl acetate, acetone, diethyl ether and heptane.

TELEXA®- M 25 is available as tablets for oral administration. Tablets containing 40 mg of Telmisartan and 25 mg of Metoprolol succinate ER (as Extended Release) are available.

PHARMACOLOGIC PROPERTIES:

PHARMACODYNAMICS

Telmisartan:

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.

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal vasopressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone- secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Telmisartan does not inhibit ACE (kininase II); it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and

angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure

In addition to blocking the RAS, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a central regulator of insulin and glucose metabolism. It is believed that telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).

Telmisartan has a PPAR-γ agonist activity. Its activity at the peroxisome proliferator-activated receptor delta (PPAR-δ) receptor has prompted speculation around its potential. Telmisartan activates PPAR-δ receptors in several tissues.

Metoprolol Succinate:

Metoprolol is a Beta1- selective (cardio selective) adrenergic receptor blocking agent, i.e. it blocks β_1– Receptors at doses lower than those needed to block β_2 -receptors.

Metoprolol is practically devoid of membrane stabilizing activity and does not display partial agonist activity (i.e. intrinsic sympathomimetic activity = ISA) at doses required to produce β-blockade. The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac output, cardiac contractility and blood pressure.

Extended release metoprolol succinate is not bioequivalent. Extended release metoprolol succinate gives an even plasma concentration time profile and effect (β_1-blockade) over 24 hours in contrast to conventional tablet formulations of β_1-selective blockers including metoprolol succinate formulations. When given together with a β_2-agonist, metoprolol succinate in therapeutic doses interferes less than non-selective β-blockers with β_2-mediated bronchodilation (see PRECAUTIONS). When clinically necessary, metoprolol succinate, in combination with a β_2-agonist, may be given to patients with symptoms of obstructive pulmonary disease. Metoprolol succinate also interferes less with insulin release than non- selective β-blockers.

PHARMACOKINETICS

Absorption

Telmisartan:

Following oral administration of telmisartan, absorption is rapid (t_{max} ranges from 0.5 to 2 hours) although the amount absorbed varies. Peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Telmisartan is quickly but to varying degrees absorbed from the gut. The average bioavailability is about 50% (42–100%). Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose.

The absolute bioavailability of telmisartan is dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%. The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses.

Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, telmisartan may be taken with or without food.

Metoprolol succinate:

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 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, across the dosage range of 50-400 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 administration.

Distribution

Telmisartan:

Telmisartan is highly bound to plasma protein (>99.5%), mainly albumin and alpha-1-acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 6.6 L/kg.

Metoprolol succinate:

TELEXA®- M consist metoprolol succinate, each coated with a polymeric membrane which controls the rate of metoprolol extended release. After rapid disintegration within the gastrointestinal tract, metoprolol is continuously released for approximately 20 hours, and a stable metoprolol plasma concentration is achieved over a dosage interval of 24 hours. Approximately 12% of metoprolol is bound to human serum proteins.

Metabolism

Telmisartan:

Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolized by the cytochrome P450 system.

Metoprolol succinate:

When administered orally, Metoprolol undergoes oxidative metabolism in the liver, primarily by CYP2D6. Due to polymorphism of CYP2D6, about 5-10% of Caucasians and a lower percentage of Asian and African populations are poor metabolizers of metoprolol. Such people experience higher plasma concentrations of metoprolol for a given dose. Because of these differences between individuals, gradual dose titration is important. Co- administration of drugs which inhibit CYP2D6 may increase plasma concentrations of metoprolol, particularly in extensive metabolizers (the majority of the population). Three main metabolites have been identified, although none have a beta-blocking effect of clinical importance.

Excretion

Telmisartan:

Telmisartan is characterized by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours. It has the longest half-life of any ARB (24 hours). 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 (CL_{tot}) is high (approximately 1000 mL/min) when compared with hepatic blood flow (about 1500 mL/min).

Metoprolol succinate:

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3-7 hours. Over 95% of an oral dose can be recovered in the urine. Only approximately 5% of the administered dose is excreted unchanged, with this figure rising to 30% in isolated cases.

SPECIAL POPULATIONS:

Telmisartan:

Elderly patients: The pharmacokinetics of telmisartan does not differ between younger and elderly patients (i.e., patients older than 65 years of age).

Patients with renal impairment: Lower plasma concentrations were observed in patients with renal insufficiency (creatinine clearance 30-80 mL/min) undergoing dialysis, however, this has proved not to be of clinical significance. Telmisartan is highly bound to plasma proteins in renal-insufficient subjects and cannot be removed by dialysis.

Patients with hepatic impairment: Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%.

Gender: Plasma concentrations are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary.

Children: There are limited data on the pharmacokinetics of telmisartan in patients less than 18 years of age.

Metoprolol succinate:

Pediatric

The pharmacokinetic profile of metoprolol extended release in 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 has not been investigated in patients.

INDICATIONS:

TELEXA®- M tablets are indicated for:

- Treatment of hypertension (High blood pressure), Heart failure and Diabetic kidney disease
- Prevention of cardiovascular morbidity and mortality in patients 55 years or older with coronary artery disease, peripheral artery disease, previous stroke, transient ischemic attack or high risk diabetes with evidence of end organ damage.

CONTRAINDICATIONS:

Telmisartan:

Telmisartan is contraindicated if,

- Hypersensitivity to any of the components of the product
- Pregnancy
- Lactation
- Biliary obstructive disorders OR Bilateral renal artery stenosis in which it can cause kidney failure
- Severe hepatic impairment
- Some drugs affecting the Renin–angiotensin system (RAS), telmisartan can cause birth defects, stillbirths, and neonatal deaths.
- The concomitant use of telmisartan with aliskirenis contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m^2)

Metoprolol succinate:

- *Predisposition to bronchospasm*

  β-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients.

  Therefore, β-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective β-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- Right ventricular failure secondary to pulmonary hypertension
- Significant right ventricular hypertrophy
- Second and third degree atrioventricular block

- Shock (including cardiogenic and hypovolaemic shock)
- Unstable decompensated congestive heart failure (pulmonary oedema, hypoperfusion or hypotension).
- Continuous or intermittent inotropic therapy acting through β-receptor agonist
- Clinically relevant sinus bradycardia (less than 45-50 beats/minute)
- Non-compensated congestive heart failure (see PRECAUTIONS)
- Sick-sinus syndrome
- Severe peripheral arterial circulatory disorders
- Suspected acute myocardial infarction with a heart rate of < 45 beats/minute, a P-R interval of > 0.24 seconds or a systolic blood pressure of < 100 mmHg, and/or moderate to severe non-compensated heart failure
- Hypotension
- Untreated phaeochromocytoma (see PRECAUTIONS)
- Hypersensitivity to any component of TELEXA®- M and related derivatives. Cross-sensitivity between β-blockers can occur.

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see PRECAUTIONS).

PRECAUTIONS:

Telmisartan:

Renal artery stenosis and kidney transplant

There are no data available on the use of telmisartan in patients who have had a kidney transplant. 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.

Increases in serum creatinine with ACE-inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with telmisartan.

Impaired renal function

When telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. 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 angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with acute hypotension, oliguria and/or progressive uraemia and rarely with acute renal failure and/or death.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported in susceptible

individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor antagonist) should therefore be limited to individually defined cases with close monitoring of renal function (see CONTRAINDICATIONS).

In the ONTARGET trial, patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of hyperkalaemia, renal failure, hypotension and syncope compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is therefore not recommended in patients with already controlled blood pressure.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor antagonist, an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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.

Diabetes Mellitus

Exploratory post-hoc analyses of two placebo-controlled telmisartan trials suggested an increased risk of fatal myocardial infarction and unexpected cardiovascular death (death occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of other etiology) in patients with diabetes mellitus who have no documented medical history of either coronary heart disease or myocardial infarction. In patients with diabetes mellitus, coronary heart disease may be asymptomatic and can therefore remain undiagnosed. Treatment with the blood pressure lowering agent telmisartan may further reduce coronary perfusion in these patients. For this reason, patients with diabetes mellitus should undergo specific diagnostics and be treated accordingly before initiating therapy with telmisartan.

Aortic and mitral valve stenosis, and obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Hyperkalaemia

During treatment with medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur, especially in the presence of renal impairment

and/or heart failure. Monitoring of serum potassium levels in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase the potassium level (e.g., heparin, etc.) may lead to an increase in serum potassium and should, therefore, be co-administered cautiously with telmisartan.

Hepatic impairment

The majority of telmisartan is eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance.

Telmisartan is, therefore, contraindicated for use in these patients. Telmisartan should only be used with caution in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION).

Sorbitol

TELEXA®-M contains sorbitol, Patients with rare hereditary condition of fructose intolerance should not take this product.

Sodium- and/or volume-depleted patients

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of telmisartan.

Use in cardiac failure

Telmisartan may be used in patients with congestive heart failure. However patients should be carefully observed for hypotension when initiating therapy.

Other

As observed for angiotensin converting enzyme inhibitors, angiotensin receptor antagonists including telmisartan 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. As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke.

Effects on Fertility

No studies on fertility in humans have been performed.

Metoprolol succinate:

Symptomatic cardiac failure

β-blockers should not be used in patients with unstabilized heart failure. This condition should first be stabilized with appropriate treatment (e.g. angiotensin- converting enzyme inhibitors, digoxin, and diuretics). If cardiac failure persists, Metoprolol succinate should be discontinued gradually (see PRECAUTIONS - Abrupt Withdrawal).

Bronchospasm

Metoprolol succinate is for patients known to be suffering from asthma; an inhaled β_2-agonist should be administered. The dosage of β_2-agonists may require adjustment (increase); however the risk of Metoprolol succinate interfering with β_2-receptors is less than with conventional tablet formulations of β_1-selective blockers.

Concomitant therapy with calcium antagonists

The concomitant use of calcium antagonists with myocardial suppressant and sinus node activity (e.g. verapamil and to a lesser extent diltiazem) and β-blockers may cause bradycardia, hypotension and a systole. Extreme caution is required if these drugs have to be used together (see INTERACTIONS WITH OTHER DRUGS).

Anti-arrhythmic drugs

Care should be taken when prescribing β-blockers with antiarrhythmic drugs as they may enhance the negative inotropic and chronotropic effects (see INTERACTIONS WITH OTHER DRUGS).

Diabetes

Metoprolol succinate should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetic patients should be warned that β-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted. Diabetic patients receiving Metoprolol succinate should be monitored to ensure diabetes control is maintained.

Other metabolic effects

Beta adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

Conduction disorders

Very rarely a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). Metoprolol succinate should be administered with caution to patients with first degree A-V block (see CONTRAINDICATIONS).

Peripheral vascular disease

β-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease (see CONTRAINDICATIONS).

Bradycardia

If patients develop increasing bradycardia, Metoprolol succinate should be given in lower doses or gradually withdrawn.

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a β-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Effects on the thyroid

The effects of β-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Phaeochromocytoma

Metoprolol succinate is for a patient known to be suffering from phaeochromocytoma; a β-blocker should be given concomitantly to avoid exacerbation of hypertension.

Effects on the eye and skin

Various skin rashes and conjunctival xerosis have been reported with β-blocking agents. Cross-reactions may occur between β-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms. During long-term treatment with the β-blocking drug practolol a specific rash bearing a superficial resemblance to psoriasis was occasionally described. In a number of the patients affected, this rash was accompanied by adverse effects on the eye (xerophthalmia and/or keratoconjunctivitis) of varying severity. This condition is called the oculomucocutaneous or practolol syndrome. On a few rare occasions, serious otitis media, sclerosing peritonitis and pleurisy have been reported as part of this syndrome.

The oculomucocutaneous syndrome as reported with practolol has not been reported with metoprolol. However, dry eyes and skin rash have been reported with metoprolol. If such symptoms occur, discontinuation of metoprolol should be considered.

Recently, an association between Peyronie's disease (a fibrosing induration of the penis) and various β-blockers has been suggested but is not proven.

General anaesthesia

Prior to surgery the anaesthetist should be informed that the patient is receiving Metoprolol succinate because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and decreased propensity for vagal-induced bradycardia (see INTERACTIONS WITH OTHER DRUGS). It is not recommended to stop β-blocker treatment in patients undergoing surgery. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

If it is thought necessary to withdraw β-blocker therapy before surgery, this should be done gradually and completed about 48 hours before surgery. (See Abrupt Withdrawal below)

Abrupt withdrawal

Abrupt withdrawal of β-blockade is hazardous, especially in high risk patients, and should not be done. If there is a need to discontinue treatment with Metoprolol succinate, this should be done gradually over at least two weeks with the dose reduced by half in each step, down to a final dose of half a 23.75 mg tablet. The final dose should be taken for at least four days before discontinuation. Close observation of the patient is required during the withdrawal phase. If symptoms occur, a slower withdrawal rate is recommended. Sudden withdrawal of β-blockade may aggravate chronic heart failure and also increase the risk of myocardial infarction and sudden death.

Allergic conditions

Allergic reactions may be exaggerated by β-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). β-blockers should be avoided if there is a risk of bronchospasm.

In patients taking β-blockers, anaphylactic shock assumes a more severe form and may be resistant to usual doses of adrenaline. Whenever possible, β-blockers should be avoided in patients who are at increased risk of anaphylaxis.

Hyperthyroidism

Because β-blockers may mask the clinical signs of developing or continuing hyperthyroidism resulting in symptomatic improvement without any change in thyroid status, special care should be exercised in hyperthyroid patients who are also receiving β-blockers. Where Metoprolol succinate is administered to patients having, or suspected of developing thyrotoxicosis, both thyroid and cardiac function should be closely monitored.

Effects on the heart rate

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/minute), the dosage of Metoprolol succinate should be gradually reduced or treatment gradually withdrawn (see CONTRAINDICATIONS).

Impaired renal function

In patients with severe renal disease haemodynamic changes following β-blockade may impair renal function further. β-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

Impaired hepatic function

Metoprolol is mainly eliminated by hepatic metabolism (see Pharmacokinetics). Therefore, liver cirrhosis may increase the systemic bioavailability of metoprolol and reduce its total clearance, leading to increased plasma levels.

Effects on fertility

There was no evidence of impaired fertility at 50 mg/kg/day.

Use in Pregnancy:

Telmisartan: Category D

Angiotensin II receptor antagonists should not be initiated during pregnancy. The use of

angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Although there is no clinical experience with telmisartan in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause foetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, telmisartan should be discontinued as soon as possible.

Telmisartan do not indicate teratogenic effect, but have shown foetotoxicity. Angiotensin II receptor antagonists exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased foetal renal function, has been associated with foetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and foetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their foetus should they become pregnant.

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension, oliguria and hyperkalaemia.

Metoprolol succinate: Category C

As with most drugs, Metoprolol succinate should not be given during pregnancy unless its use is considered essential. As with all antihypertensive agents, β-blockers may cause side effects (e.g. reduced placental perfusion and bradycardia) in the foetus and newborn. During the late stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the foetus.

The lowest possible dose should be used and discontinuation of treatment should be considered at least 2 to 3 days before delivery to avoid increased uterine contractility and effects of β-blockade in the newborn (e.g. bradycardia, hypoglycaemia).

Use in Lactation

Telmisartan:

Telmisartan is contraindicated during lactation since it is not known whether it is excreted in human milk. No clinical trials have been carried out in lactating women. Therefore, lactating women should either not be prescribed telmisartan or should discontinue breastfeeding, if telmisartan is administered.

Metoprolol succinate:

As with most drugs, Metoprolol succinate should not be given during lactation unless its use is considered essential. As with all antihypertensive agents, β-blockers may cause side effects (e.g. bradycardia), in the breast-fed infant. The amount of metoprolol ingested via breast-milk seems to be negligible, in regard to β-blocking effect in the infant, if the mother is treated with metoprolol in doses within the normal therapeutic range.

Use in Children

Telmisartan:

The safety and efficacy of telmisartan for use in children below 18 years have not been established.

Metoprolol succinate:

The safety and efficacy of metoprolol in children has not been established.

Effects on ability to drive and use machines

Telmisartan:

There are no data to suggest that telmisartan affects the ability to drive and use machines. However, when driving or operating machinery it should be taken into account that with antihypertensive therapy, occasionally dizziness or drowsiness may occur.

Metoprolol succinate:

Metoprolol succinate may occasionally cause dizziness, visual disturbances or fatigue (see ADVERSE REACTIONS), hence patients should know how they react to Metoprolol succinate before they drive or use machinery, particularly when starting or changing treatment.

Carcinogenicity

Telmisartan:

Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Metoprolol succinate:

There was no increase in the incidence of neoplasms. It increased incidence of focal accumulation of foamy macrophages in pulmonary alveoli and an increased incidence of biliary hyperplasia.

Genotoxicity

Telmisartan & Metoprolol succinate:

Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

INTERACTIONS WITH OTHER MEDICINES:

Telmisartan:

Telmisartan may increase the hypotensive effect of other antihypertensive agents.
Other interactions of clinical significance have not been identified. Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine.

Telmisartan increases blood potassium levels. Combination with potassium preparations or potassium-sparing diuretics could cause hyperkalaemia (excessive potassium levels). When telmisartan was co-administered with digoxin, an increase in digoxin AUC (22%), C_{max} (50%), and C_{min} (13%) values was observed. It is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under- digitalization.

The co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1 fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function (see also PRECAUTIONS).
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Careful monitoring of serum lithium levels is recommended during concomitant use.

Treatment with NSAIDs (i.e. aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Combination with NSAIDs, especially in patients with impaired kidney function, has a risk of causing (usually reversible) kidney failure. Compounds acting on the renin-angiotensin system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit, or are metabolized by, cytochrome P450 enzymes.

Metoprolol succinate:

CYP2D6 Inhibitors

Co-administration of drugs which inhibit CYP2D6 such as quinidine, fluoxetine and paroxetine may cause increased exposure to metoprolol and consequent increased pharmacological effects. Concomitant administration of the CYP2D6 inhibitor quinidine has been shown to substantially increase systemic exposure of both enantiomers of metoprolol. 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. These increases in plasma concentration are highly likely to be associated with exaggerated pharmacological effects and decrease in the cardioselectivity of metoprolol.

Interactions with hydroxychloroquine and diphenhydramine, although smaller, could still be clinically significant.

Other anti-hypertensive agents

Metoprolol enhances the effects of other antihypertensive drugs. Particular care is required when initiating administration of a β-blocker and prazosin together.

Sympathetic ganglion blocking agents, other β-blockers or monoamine oxidase (MAO) inhibitors

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other β-blockers (including eye drops), or monoamine oxidase (MAO) inhibitors should be kept under close surveillance.

Clonidine

Concurrent use of β-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms.

If concomitant treatment with clonidine is to be discontinued, the β-blocker medication should be withdrawn several days before the gradual withdrawal of clonidine. The rebound hypertension associated with clonidine withdrawal can be exacerbated by the presence of a β-blocker. If both drugs are withdrawn simultaneously, a marked rise in blood pressure and/or arrhythmias may result.

If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped.

Calcium antagonists

If Metoprolol succinate is given with calcium antagonists of the verapamil and diltiazem type the patient should be monitored for possible negative inotropic and chronotropic effects. Calcium antagonists of the phenylalkylamine type (e.g. verapamil) should not be given by intravenous administration to patients treated with metoprolol because there is a risk of cardiac arrest in this situation. Patients taking oral calcium antagonists of this

type in combination with metoprolol should be closely monitored.

The combination of β-blockers with dihydropyridine calcium channel blockers with a weak myocardial depressant effect (e.g. felodipine, nifedipine) can be administered together with caution. In case excess hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

Antiarrhythmic agents

When metoprolol is given together with antiarrhythmic agents, the patients should be monitored for possible negative inotropic and chronotropic effects. The negative inotropic and negative chronotropic effects of antiarrhythmic agents of the quinidine type and amiodarone may be enhanced by β-blockers. Interactions have been reported during concomitant β-blocker therapy with the Class IA agents, disopyramide, and less frequently quinidine; class IB agents, tocainide, mexiletine and lignocaine; the Class IC agent flecainide; the Class III agent amiodarone; and the Class IV antiarrhythmic agents (e.g. verapamil).

Anaesthetics

In patients receiving β-blocker therapy, inhalation anaesthetics enhance the cardiodepressant effect (see PRECAUTIONS). Metoprolol may also reduce the clearance of other drugs (e.g. lignocaine). Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, and trichlorethylene) were sometimes associated with severe circulatory depression in the presence of β-blockage.

Liver enzyme effects

Enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by cimetidine, alcohol, hydralazin, and selective serotonin re-uptake inhibitors (SSRIs) e.g. paroxetine, fluoxetine, and sertraline, quinidine, verapamil and diphenhydramine.

Prostaglandin synthetase inhibiting agents

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of β-blockers.

Alcohol

Metoprolol may modify the pharmacokinetic behaviour of alcohol when taken together. The plasma level of metoprolol may be raised by alcohol.

Oral antidiabetic agents

The dosages of oral antidiabetics may need to be adjusted in patients receiving β-blockers. (see PRECAUTIONS).

Warfarin

A limited number of reports have demonstrated a rise in AUC and concentration of warfarin when taken with another β-blocker. This could potentially increase the anti-coagulant effect of warfarin.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs such as reserpine, mono amine oxidase (MAO) inhibitors and guanethidine have an additive effect when given with β-blocking agents. Patients treated with Metoprolol succinate plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension, since the added effect of a β-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

Digitalis glycosides

Digitalis glycosides, in association with β-blockers, may increase atrioventricular conduction time and may induce bradycardia.

ADVERSE EFFECTS

Telmisartan:

Adverse reactions have usually been mild and transient in nature and have only infrequently required discontinuation of therapy. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients.

After the first dose of telmisartan, the incidence of symptomatic orthostatic hypotension with symptoms severe enough to be reported as an adverse event

It cannot be determined whether these events were causally related to telmisartan tablets:

Infections and infestations: upper respiratory tract infections (including rhinitis), bronchitis, urinary tract infections (including cystitis), infection, fungal infection, abscess, otitis media

Immune system disorders: allergy
Metabolism and nutrition disorders: gout, hypercholesterolaemia, diabetes mellitus
Psychiatric disorders: anxiety, insomnia, depression, nervousness
Nervous system disorders: somnolence, migraine, paraesthesia, hypoaesthesia
Eye disorders: visual disturbance, conjunctivitis
Ear and labyrinth disorders: vertigo, tinnitus, earache
Cardiac disorders: tachycardia, bradycardia, palpitation, angina pectoris
Vascular disorders: hypotension, flushing, cerebrovascular disorder
Respiratory disorders: dyspnoea, asthma, epistaxis
Gastrointestinal disorders: dry mouth, flatulence, stomach discomfort, vomiting, constipation, gastritis, haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache
Skin and subcutaneous tissue disorders: eczema, pruritus, hyperhidrosis, rash, dermatitis
Musculoskeletal, connective tissue and bone disorders: arthralgia, involuntary muscle contractions or muscle spasms (cramps in legs) or pain in extremity (leg pain), arthritis
Renal and urinary tract disorders: micturition frequency
Reproductive system and breast disorders: impotence

General disorders and administration site conditions: malaise, fever, leg oedema, dependent oedema
Investigations: abnormal

ECG LABORATORY FINDINGS

No significant differences in changes in laboratory test parameters were observed in clinical studies with telmisartan.

Hemoglobin decreased**:** A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anaemia.

Blood creatinine increased**:** A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hepatic enzymes increased**:** Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Prevention of cardiovascular morbidity and mortality:

Because common adverse reactions were well characterized with telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were found with telmisartan in the prevention of cardiovascular morbidity and mortality.

The safety profile of telmisartan in patients treated for the prevention of cardiovascular morbidity and mortality was consistent with that obtained in hypertensive patients.

Patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported.

Post-Marketing Experience:

In addition, the following have also been reported since the introduction of telmisartan in the market:

Blood and lymphatic system disorders:
Uncommon: anaemia
Rare: eosinophilia, thrombocytopenia

Immune system disorders:
Rare: anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:
Uncommon: hyperkalaemia
Rare: hypoglycemia (in diabetic patients)

Nervous system disorders:
Uncommon: syncope (faint)

Cardiac disorders:
Uncommon: bradycardia

Vascular disorders:
Uncommon: hypotension, orthostatic hypotension

Hepatobiliary disorders:
Rare: hepatic function abnormal / liver disorder*
* Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.

Skin and subcutaneous tissue disorders:
Rare: angioedema (with fatal outcome), erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders:
Rare: tendon pain (tendinitis like symptoms)

Renal and urinary tract disorders:
Uncommon: renal impairment including acute renal failure (see PRECAUTIONS)

General disorders and administration site conditions:
Uncommon: asthenia (weakness)

Investigations:
Uncommon: blood uric acid increased, blood creatinine phosphokinase (CPK) increased

Metoprolol succinate:

Metoprolol succinate is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events reported from routine use, mostly with conventional metoprolol. In many cases a relationship with metoprolol has not been established.

The following definitions of frequency are used: very common ≥10%; common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare <0.01%.

Cardiovascular

Common:	Bradycardia, postural disorders (very rarely with syncope), cold hands and feet (Raynaud's phenomenon), palpitations.
Uncommon:	Transient deterioration of heart failure symptoms, A-V blocks I, oedema, precordial pain, cardiogenic shock in patients with acute myocardial infarction.
Rare:	Disturbances of cardiac conduction, cardiac arrhythmias.
Very rare:	Gangrene in patients with pre-existing severe peripheral circulatory disorders.

Central nervous system

Very common:	Fatigue
Common:	Dizziness, headache.
Uncommon:	Paraesthesia, muscle cramps.

Gastrointestinal

Common: Nausea, diarrhoea, constipation, abdominal pain. Uncommon: Vomiting

Rare: Dry mouth

Haematologic

Very rare: Thrombocytopenia

Hepatic

Rare: Liver function test abnormalities

Very Rare: Hepatitis

Metabolic

Uncommon: Weight gain

Psychiatric

Uncommon: Depression, impaired concentration, somnolence or insomnia, ` nightmares.

Rare: Nervousness, anxiety, impotence / sexual dysfunction.

Very rare: Amnesia / memory impairment, confusion, hallucinations.

Respiratory

Common: Dyspnoea on exertion

Uncommon: Bronchospasm (which may also occur in patients without a history of obstructive lung disease)

Rare: Rhinitis

Sense organs

Rare: Disturbances of vision, dry and/or irritated eyes, conjunctivitis. Very rare: Tinnitus, taste disturbances.

Skin

Uncommon: Rash (in the form of urticaria, psoriasiform and dystrophic skin lesions) increased sweating.

Rare: Loss of hair

Very rare: Photosensitivity reactions, aggravated psoriasis.

Miscellaneous

Very rare: Arthralgia

DOSAGE AND ADMINISTRATION

Telmisartan:

Treatment of Hypertension:

***Adults*:** The recommended dose is 40-80 mg once daily. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to 80 mg once daily. Telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that,

while reduction in blood pressure is achieved after the first dose, the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Prevention of cardiovascular morbidity and mortality

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in preventing cardiovascular morbidity and mortality.

When initiating telmisartan therapy for the prevention of cardiovascular morbidity and mortality, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary.

Metoprolol succinate may be administered with or without food.

***Elderly*:** No dosing adjustment is necessary.

***Renal impairment*:** No dose adjustment is required for patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by haemofiltration.

***Hepatic impairment*:** In patients with mild to moderate hepatic impairment, the dosage should not exceed 40 mg once daily (see PRECAUTIONS).

Metoprolol succinate:

Metoprolol succinate has not been established to be clinically equivalent to immediate release forms of metoprolol, and should not be used for treatment of conditions other than stable, chronic heart failure.

Metoprolol succinate is recommended for once daily treatment and is preferably taken together with the morning meal.

The patient should be carefully evaluated at each dose level with regard to tolerability. If the patient experiences hypotension a decreased dose of concomitant heart failure medication may be necessary. Initial hypotension does not necessarily mean that the dose cannot be tolerated during chronic treatment but the patient should be kept at the lower dose until their blood pressure has stabilized.

Impaired renal and hepatic function

Dose adjustment is not needed in patients with impaired renal function.

Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol is low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g. patients who have had a shunt operation), a dose reduction should be considered.

Elderly: Dose adjustment is not needed in the elderly.

Children: There is limited experience with Metoprolol succinate in children.

OVERDOSAGE

Telmisartan:

Limited information is available with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia

also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

Metoprolol succinate:

Symptoms

Overdosage of Metoprolol succinate may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, convulsions, nausea, vomiting, and cyanosis.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first manifestations of overdose may be observed 20 minutes to 2 hours after the drug is ingested.

Management

Induction of vomiting or gastric lavage. In the presence of severe hypotension, bradycardia, and impending heart failure; administer a β_1-agonist (e.g. isoprenaline) intravenously at 2-5 minute intervals or as continuous infusion until the desired effect is achieved. Where a selective β_1-agonist is not available, dopamine or atropine sulphate i.v. may be used in order to block the vagus nerve. If a satisfactory effect is not achieved, other sympathomimetic agents, such as dobutamine may be used, or noradrenaline may be given.

Glucagon in a dose of 1-10 mg can also be administered. Glucagon activates the adenylcyclase system independently of the β-receptor, augmenting the contractility in the presence of β-blockade. A pacemaker may be necessary.

To combat bronchospasm, a β_2-agonist can be given intravenously.

Observe that the dosage of drugs (antidotes) needed to treat overdose of β-blockade are much higher than normally recommended therapeutic dosages. This is because β-receptors are occupied by the β-blocker.

STORAGE CONDITION: Store below 25°C in dry place. Keep out of reach of children.

PRESENTATION: Telmisartan 40 mg + Metoprolol Succinate 25 mg ER Tablets

PACKING: 1*10 TAB

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

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