

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

TELDAY M 50

Telmisartan and Metoprolol Succinate (ER) Tablets

COMPOSITION

Each Film coated bi-layered tablet contains:

Telmisartan I.P. 40 mg

Metoprolol Succinate U.S.P. 47.50 mg equivalent to Metoprolol Tartrate 50 mg

(As extended release form)

Colour: Lake of Sunset Yellow

WARNING: FETAL TOXICITY

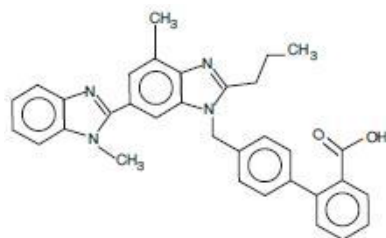
When pregnancy is detected, discontinue the product as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

DESCRIPTION

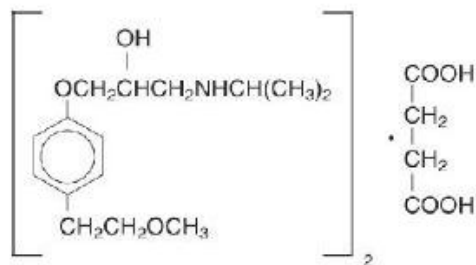
Telmisartan

Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan is chemically described as 4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H benzimidazol -1-yl]methyl]biphenyl-2-carboxylic acid. Its empirical formula is C₃₃H₃₀N₄O₂. Its molecular weight is 514.6 and its structural formula is:



Metoprolol succinate

Metoprolol succinate is Beta receptor blocker. Its chemical name is (±)1(isopropylamino)-3- [p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. Its structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Telmisartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor 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 AT₁ 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 AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT₁ receptor than for the AT₂ 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. Because 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.

Metoprolol succinate

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

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

Pharmacodynamics

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours. Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

Metoprolol succinate

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

Metoprolol is a beta₁-selective (cardioselective) 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 membranestabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

The relative beta₁-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta₂ - mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-receptor blocking doses.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an E_{max} model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to beta₁ - blockade. Beta₁ - blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative beta₁ - selectivity of metoprolol diminishes and blockade of beta₂ - adrenoreceptors increases at plasma concentration above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta₂ - adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In other studies, treatment with metoprolol produced an improvement in left ventricular ejection fraction. metoprolol was also shown to delay the increase in left ventricular endsystolic and end-diastolic volumes after 6 months of treatment.

Pharmacokinetics

Telmisartan

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5 to 1 hour after dosing. 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. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 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% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism and Elimination

Following either intravenous or oral administration of ^{14}C -labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Specific populations

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration [see Warnings and Precautions and Dosage and Administration].

Hepatic Insufficiency In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased and absolute bioavailability approaches 100% [see Warnings and Precautions and Use in Specific Populations].

Gender

Plasma concentrations of telmisartan are generally 2 to 3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Geriatric Patients

The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years [see Dosage and Administration].

Pediatric Patients

Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Metoprolol succinate

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

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits 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 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity [see *Drug Interactions*].

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of metoprolol are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once-daily administration of metoprolol average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of metoprolol, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, β_1 -blockade is comparable and dose-related [see *Clinical Pharmacology*]. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following administration.

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

NONCLINICAL TOXICOLOGY

Telmisartan

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Developmental Toxicity

There is no clinical experience with the use of telmisartan tablets in pregnant women. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food

consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m² basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m² basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m² basis, the maximum recommended human dose of telmisartan (80 mg/day).

Metoprolol succinate

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60kg patient.

CLINICAL STUDIES

Telmisartan

Hypertension

The antihypertensive effects of telmisartan have been reported in six principal placebocontrolled clinical trials, studying a range of 20 to 160 mg; one of these examined the antihypertensive effects of telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95 to 114 mmHg), 1031 of whom were treated with telmisartan. Following once daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with telmisartan tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year. The antihypertensive effect of telmisartan is not influenced by patient age, gender, weight, or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.

In a controlled study, the addition of telmisartan to hydrochlorothiazide produced an additional dose-related reduction in blood pressure that was similar in magnitude to the reduction achieved with telmisartan monotherapy. Hydrochlorothiazide also had an added blood pressure effect when added to telmisartan.

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40 to 80 mg doses of telmisartan was 70 to 100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with telmisartan in controlled trials.

There are no trials of telmisartan demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

Metoprolol succinate

In five controlled studies in normal healthy subjects, the same daily doses of metoprolol and immediate-release metoprolol were compared in terms of the extent and duration of beta₁-blockade produced. Both formulations were given in a dose range equivalent to 100-400 mg of immediate-release metoprolol per day. In these studies, METOPROLOL was administered once a day and immediate-release metoprolol was administered once to four times a day. A sixth controlled study compared the beta₁-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta₁-blockade was expressed as the percent change from baseline in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. metoprolol administered once a day, and immediate-release metoprolol administered once to four times a day, provided comparable total beta₁-blockade over 24 hours (area under the beta₁-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, metoprolol produced significantly higher total beta₁blockade over 24 hours than immediate-release metoprolol. For metoprolol, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta₁-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (ie, at 24-hours post-dosing) were: 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg metoprolol once a day, respectively. In contrast to metoprolol,

immediate-release metoprolol given at a dose of 50-100 mg once a day produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with metoprolol over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate-release metoprolol. A controlled cross-over study in heart failure patients compared the plasma concentrations and beta₁-blocking effects of 50 mg immediate-release metoprolol administered t.i.d., 100 mg and 200 mg metoprolol once daily. A 50 mg dose of immediate-release metoprolol t.i.d. produced a peak plasma level of metoprolol similar to the peak level observed with 200 mg of metoprolol. A 200 mg dose of metoprolol produced a larger effect on suppression of exercise-induced and Holter monitored heart rate over 24 hours compared to 50 mg t.i.d. of immediate-release metoprolol.

In a double-blind study, 1092 patients with mild-to-moderate hypertension were randomized to once daily metoprolol (25, 100, or 400 mg), felodipine extended-release tablets, the combination, or placebo. After 9 weeks, metoprolol alone decreased sitting blood pressure by 6-8/4-7 mmHg (placebo-corrected change from baseline) at 24 hours post-dose. The combination of metoprolol with felodipine extended-release tablets has greater effects on blood pressure.

In controlled clinical studies, an immediate-release dosage form of metoprolol was an effective antihypertensive agent when used alone or as concomitant therapy with thiazidetype diuretics at dosages of 100-450 mg daily. metoprolol, in dosages of 100 to 400 mg once daily, produces similar β₁-blockade as conventional metoprolol tablets administered two to four times daily. In addition, metoprolol administered at a dose of 50 mg once daily lowered blood pressure 24-hours post-dosing in placebo-controlled studies. In controlled, comparative, clinical studies, immediate-release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyl dopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

INDICATIONS

For the treatment of essential hypertension

DOSAGE AND ADMINISTRATION

As directed by the physician Tablet to be swallowed whole, not to be crushed, chewed or broken.

CONTRAINDICATIONS

Telmisartan

Telmisartan is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or any other component of this product [see Adverse Reactions].

Metoprolol succinate

Metoprolol is contraindicated in severe bradycardia, second or third degree heart block, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

WARNINGS AND PRECAUTIONS

WHEN PREGNANCY IS DETECTED PRODUCT SHOULD BE DISCONTINUED AS SOON AS POSSIBLE AS IT CAN CAUSE INJURY AND EVEN DEATH TO THE DEVELOPING FOETUS, WHEN USED DURING THE SECOND AND THIRD TRIMESTERS OF PREGNANCY.

Telmisartan

Fetal Toxicity Pregnancy Category D

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 detected, discontinue telmisartan as soon as possible [*see Use in Specific Populations*].

Hypotension

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan. Either correct this condition prior to administration of telmisartan, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Impaired Hepatic Function

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients [*see Use in Specific Populations*) and *Clinical Pharmacology*].

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with telmisartan [*see Clinical Pharmacology*].

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The reported ONTARGET trial enrolled 25,620 patients ≥ 55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on telmisartan and other agents that affect the RAS.

Do not co-administer aliskiren with telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with telmisartan in patients with renal impairment ($\text{GFR} < 60 \text{ mL/min/1.73 m}^2$).

Metoprolol succinate

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, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate metoprolol, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing metoprolol in patients treated only for hypertension.

Heart Failure

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

Bronchospastic Disease

Patients with bronchospastic diseases should, in general, not receive beta - blockers.

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

Pheochromocytoma

If metoprolol is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Major Surgery

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

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

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

Hepatic Impairment

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

Thyrotoxicosis

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

Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Peripheral Vascular Disease

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

Calcium Channel Blockers Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

DRUG-INTERACTIONS

Telmisartan

Aliskiren: Do not co-administer aliskiren with telmisartan in patients with diabetes. Avoid use of aliskiren with telmisartan in patients with renal impairment (GFR <60 mL/min).

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Ramipril and Ramiprilat: 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. When coadministering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. 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 cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Metoprolol succinate

Catecholamine Depleting Drugs

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

CYP2D6 Inhibitors

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

Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia. If clonidine and a beta blocker, such as metoprolol are coadministered, withdraw the betablocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped [*see Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS

Telmisartan

Pregnancy Category D

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 detected, discontinue telmisartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue telmisartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus

has sustained irreversible injury. Closely observe infants with histories of in utero exposure to telmisartan for hypotension, oliguria, and hyperkalemia [see *Use in Specific Populations*].

Nursing Mothers

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Neonates with a history of in utero exposure to Telmisartan: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Safety and effectiveness in pediatric patients have not been established [see Clinical Pharmacology].

Geriatric Use

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.

Of the total number of patients receiving telmisartan in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥ 65 to < 75 years of age was 42%; 15% of patients were ≥ 75 years old. 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.

Hepatic Insufficiency

Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency [see Warnings and Precautions].

Metoprolol succinate

Pregnancy

Pregnancy Category C Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Consider possible infant exposure when metoprolol is administered to a nursing woman.

Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of metoprolol (0.2, 1.0 or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

- Dose-response for reduction in DBP,
- 1.0 mg/kg vs. placebo for change in SBP, and
- 2.0 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals [*see Dosage and Administration*].

No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of metoprolol have not been established in patients < 6 years of age.

Geriatric Use

Clinical studies of metoprolol in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

Of the 1,990 patients with heart failure randomized to metoprolol in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse reactions between older and younger patients.

In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No studies have been performed with metoprolol in patients with hepatic impairment. Because metoprolol is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

Renal Impairment The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure [see *Clinical Pharmacology*].

ADVERSE REACTIONS

Telmisartan

Renal dysfunction upon use with ramipril [see Warnings and Precautions]

Hypertension

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy. In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of $\geq 1\%$ in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Table Adverse Events Occurring at an Incidence of $\geq 1\%$ in Patients Treated with telmisartan and at a Greater Rate than Patients Treated with Placebo

	Telmisartan n=1455 (%)	Placebo n=380 (%)
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of $\geq 1\%$ but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets:

Autonomic Nervous System: impotence, increased sweating, flushing; *Body as a Whole:* allergy, fever, leg pain, malaise

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; *CNS:* insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders.

Metabolic: gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: arthritis, arthralgia, leg cramps.

Psychiatric: anxiety, depression, nervousness; *Resistance Mechanism:* infection, fungal infection, abscess, otitis media.

Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis.

Skin: dermatitis, rash, eczema, pruritus.

Urinary: micturition frequency, cystitis.

Vascular: cerebrovascular disorder.

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: 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 because of anemia.

Creatinine: 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 because of increases in creatinine and blood urea nitrogen.

Liver Enzymes: 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 because of abnormal hepatic function.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of telmisartan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan. .

The most frequent spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome).

Metoprolol succinate

The following adverse reactions are described elsewhere in labeling:

- Worsening angina or myocardial infarction
- Worsening heart failure
- Worsening AV block.

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 or immediate-release metoprolol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Respiratory: Wheezing (bronchospasm), dyspnea.

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

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

Hypersensitive Reactions: Pruritus.

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance . Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered +potential adverse reactions to metoprolol .

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.

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with telmisartan tablets 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.

Metoprolol succinate

Signs and Symptoms - Overdosage of metoprolol 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.

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

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

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

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

Bronchospasm: Administer a beta₂-agonist, including albuterol inhalation, or an oral theophylline derivative.

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

EXPIRY

Do not use later than the date of expiry.

STORAGE

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

PRESENTATION

Telday M 50 is available as blister pack of 10 tablets

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/TELDAY M 50,40mg/SEPT-15/04/PI