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

METOCARD-CHT

1. **Generic Name**

   Telmisartan, Chlorthalidone and Metoprolol ER Tablets

2. **Qualitative and quantitative composition**

   METOCARD- CHT 25

   Each film coated bilayered tablet contains:

   Telmisartan I.P. …….....40 mg

   Chlorthalidone I.P. …….……12.5 mg

   Metoprolol Succinate I.P …….....23.75 mg

   Equivalent to Metoprolol tartrate ……25 mg

   (As Extended Release)

   Excipients…….q.s.

   Colours: Quinoline yellow lake & Titanium Dioxide I.P

   METOCARD- CHT 50

   Each film coated bilayered tablet contains:

   Telmisartan I.P. …….....40 mg

   Chlorthalidone I.P. …….……12.5 mg

   Metoprolol Succinate I.P ……..... 47.5 mg

   Equivalent to Metoprolol tartrate ……50 mg

   (As Extended Release)

   Excipients…….q.s.

   Colours: Quinoline yellow lake & Titanium Dioxide I.P

   The excipients used are Dibasic Calcium phosphate, Methocel K100 Premium CR, Titanium dioxide, Acrypol 971-P, Isopropyl Alcohol, Purified Water, Talc Powder, Magnesium Stearate, Carbopol 71G, Meglumine, Microcrystalline Cellulose, Croscarmellose Sodium, Quinoline Yellow Lake, Sodium Hydroxide Pellets, Methylene Chloride, Crospovidone (XL10), Instacoat Transparent (ICS-329).

3. Dosage form and strength

Dosage Form: Film coated tablets

Strength: Telmisartan 40mg, Chlorthalidone 12.5mg and Metoprolol Tartrate 25 mg

Telmisartan 40mg, Chlorthalidone 12.5mg and Metoprolol Tartrate 50 mg

4. Clinical particulars

4.1 Therapeutic indication

METOCARD-CHT is indicated for the treatment of essential hypertension with stable coronary artery disease.

4.2 Posology and method of administration

The usual initial dosage is one tablet of METOCARD-CHT orally once daily. The dose may be increased to two tablets of METOCARD-CHT daily according to physician's discretion if blood pressure remains uncontrolled after 2-4 weeks of therapy.

Patients with Renal Impairment
The usual regimens of therapy with Telmisartan and Chlorthalidone may be followed as long as the patient's creatinine clearance is more than 30 mL/min. In patients with more severe renal impairment, Telmisartan and Chlorthalidone is not recommended.

Patients with Hepatic Impairment
Telmisartan and Chlorthalidone is not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic impairment should have treatment started with Telmisartan and Chlorthalidone under close medical supervision.

4.3 Contraindications

METOCARD-CHT is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, chlorthalidone, metoprolol or any other component of this product. Because of the chlorthalidone component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Do not co-administer aliskiren with METOCARD-CHT in patients with diabetes.

4.4 Special warnings and precautions for use

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.

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.
Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision.
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.

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.
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.
In 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 (GFR <60 mL/min/1.73 m2).

Chlorthalidone

Fetal Toxicity
Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia.

Impaired Renal Function
In patients with renal disease, chlorthalidone may precipitate azotemia. If progressive renal impairment becomes evident, as indicated by increased blood urea nitrogen, consider withholding or discontinuing diuretic therapy.

Hypokalemia
Hypokalemia is a dose-dependent adverse reaction that may develop with chlorthalidone. Coadministration of digitalis may exacerbate the adverse effects of hypokalemia.

Hyperuricemia
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone or other thiazide diuretics.

Metoprolol

Beta blockers must be administered with caution to asthmatics. If an asthmatic uses a beta-2 agonist (as tablets or by inhalation) when initiating metoprolol treatment, the dose of the beta-2 agonist must be controlled and increased if necessary.

Metoprolol may reduce the effect of diabetes treatment and mask the symptoms of hypoglycaemia.

AV conduction disorders may be aggravated in rare cases in connection with metoprolol treatment (possible atrioventricular block). Beta-blockers should be given only with caution to patients with first degree atrioventricular block.

Metoprolol may exacerbate the symptoms of peripheral vascular disorders due to its antihypertensive effect.

When prescribing metoprolol to patients with a pheochromocytoma, an alpha blocker must be used before initiating treatment and during the metoprolol treatment.

In patients with Prinzmetal's angina β1 selctive agents should be used with care because may increase the number and duration of angina attacks.

Metoprolol treatment may possibly mask the symptoms of thyreotoxicosis. Therefore, metoprolol should be administered with caution to patients having or suspected of developing thyreotoxicosis and both thyroid and cardiac functions should be monitored closely.

Before surgery, the anaesthesiologist must be informed that the patient takes beta blockers. It is not recommended to discontinue beta blocker treatment during a surgical procedure.

Beta blocker treatment must not be suddenly discontinued. If the treatment is to be discontinued, it must, where possible, be gradually reduced over a period of at least two weeks

during which the dose is withdrawn gradually, the doses diminishing to 25 mg for the last 6 days before the treatment is discontinued. If the patient presents with any symptoms, the dose should be reduced at a lower rate. Sudden discontinuation of beta blockers may possibly exacerbate heart failure and increase the risk of myocardial infarction and sudden death.

Like other beta blockers, metoprolol may also increase both the sensitivity to allergens and the severity of anaphylactic reactions. Adrenalin treatment does not always give the desired therapeutic effect in individuals receiving beta blockers.

Beta blockers may trigger or exacerbate psoriasis.

Up to the present, there is insufficient data from the use of metoprolol in patients with heart failure and the following accompanying factors:
- Unstable heart failure (NYHA IV).
- Acute myocardial infarction or unstable angina pectoris in the preceding 28 days.
- Impaired renal function.
- Impaired hepatic function.
- Patients above the age of 80.
- Patients under the age of 40.
- Haemodynamically significant valve diseases.
- Hypertrophic obstructive cardiomyopathy.
- During or after cardiac surgery within the last four months before treatment with metoprolol.

In the case of increasing bradycardia the dosage should be reduced, or treatment gradually discontinued.

Metoprolol may not be administered to patients with untreated congestive heart failure. The congestive heart failure needs to be brought under control first of all. If concomitant digoxin treatment is taking place, it must be borne in mind that both medicinal products slow AV conduction and that there is therefore a risk of AV dissociation. In addition, mild cardiovascular complications may occur, manifesting as dizziness, bradycardia, and a tendency to collapse.

Dry eyes either alone or, occasionally, with skin rashes has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

4.5 Drugs 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 40 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3- and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering 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.

Chlorthalidone

Lithium renal clearance is reduced by diuretics, such as chlorthalidone, increasing the risk of lithium toxicity.

Antidiabetic Drugs (Oral Agents and Insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Pressor Amines (eg, Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, NonDepolarizing (eg, Tubocurarine): Possible increased responsiveness to the muscle relaxant.

Metoprolol

Barbituric acid derivatives: Barbiturates (studied for pentobarbital) induce the metabolism of metoprolol through enzyme induction.

Propafenon:When propafenon was commenced in four patients, who were then treated with metoprolol, the plasma concentrations of metoprolol increased 2-5-fold and two patients suffered typical metoprolol side effects. The interaction was confirmed in a study involving eight healthy research subjects. The interaction is probably due to the fact that propafenon, like quinidine, inhibits the metabolism of metoprolol via cytochrome P450 2D6. The combination is probably difficult to manage due to the fact that propafenon also has beta-receptor blocking properties.

Calcium antagonists: In the case of the concomitant use of calcium antagonists of the verapamil or diltiazem types, an increase in negative inotropic and chronotropic effects can occur. Calcium antagonists of the verapamil type should not be administered intravenously to patients who are being treated with beta blockers, due to the risk of hypotension, AV conduction disturbances, and left ventricular insufficiency (see section 4.3). In patients with impaired cardiac function, the combination is contraindicated. As with other beta-blockers, concomitant therapy with dihydropyridines (such as nifedipine and amlodipine), may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

The following combinations with metoprolol may require dose adjustment:

Amiodarone: One case history indicates that patients treated with amiodarone can develop severe sinus bradycardia during concomitant treatment with metoprolol. Amiodarone has an extremely long half-life (approximately 50 days), which means that interactions can occur a long time after discontinuation of the preparation.

Class I-antiarrhythmics: Class I-antiarrhythmics and beta-receptor blockers have additive negative inotropic effects, which can result in serious haemodynamic adverse reactions in patients with impaired left-ventricular function. The combination should be avoided in “sick sinus syndrome” and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory drugs/antirheumatic agents (NSAID): NSAID-type antiphlogistics counteract the antihypertensive effect of beta-receptor blocking agents. Studies have primarily been performed on indomethacin. This interaction is not believed to occur with sulindac. It has not been possible to demonstrate such an interaction in a study relating to diclofenac.

CYP2D6 inhibitors: Metoprolol is a CYP2D6-substrate. Drugs which inhibit this enzyme may increase the plasma concentration of metoprolol. Examples of clinically significant inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine. On commencement of treatment with these medicinal products in patients being treated with metoprolol the dose of metoprolol may need to be reduced.

Diphenhydramine: Diphenhydramine reduces (2.5 times) clearance of metoprolol to alpha-hydroxymetoprolol in fast hydroxylaters via CYP 2 D6, at the same time as the effects of metoprolol are increased.

Digitalis glycosides: Digitalis glycosides in connection with beta-receptor blockers, can increase the atrioventricular conduction time and induce bradycardia.

Epinephrine: A dozen reports exist in respect of severe hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propanalol), who were administered epinephrine (adrenaline). These clinical observations have been confirmed in studies on healthy research subjects. It has also been suggested that epinephrine, administered as local anaesthesia, may give rise to these reactions on intravasal administration. The risk should be considerably less with cardioselective beta-receptor blockers.

Phenylpropanolamine: Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological levels in healthy research subjects. In general, propanolol counteracts the rise in blood pressure triggered by phenylpropanolamine. Beta-receptor blockers may, however, trigger paradoxical hypertensive reactions in patients taking high doses of phenylpropanolamine. Hypertensive crises during treatment solely with phenylpropanolamine have been described in a couple of cases.

Quinidine: Quinidine inhibits the metabolism of metoprolol in so-called "fast hydroxylaters" (just over 90% in Sweden), with significantly increased plasma values and resultant increase in beta blockade. Similar reaction might be expected to occur with other beta-blockers which are metabolized by the same enzyme (cytochrome P450 2 D6).

Sympathetic ganglion blockers, or other beta blockers: Patients who are concomitantly receiving sympathetic ganglion blockers, or other beta blockers (including in the form of eye drops) must continue being monitored.

MAO inhibitors: MAO inhibitors should be used with caution as concomitant administration with beta-blockers may result in bradycardia and an enhanced hypotensive effect. Monitoring of blood pressure and heart rate are recommended during initial use.

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

The concomitant use of clonidine with a non-selective beta blocker, and possibly also with a selective beta blocker, increases the risk of rebound hypertension. If clonidine is administered concomitantly, the administration of the clonidine medication needs to be continued for some time after beta-blocker therapy is discontinued.

Paroxetine: may increase plasma levels of metoprolol resulting in increased beta-blocking effects

Ergotamine: As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity, e.g. ergotamine are given concurrently

Nitrates: Nitrates may enhance the hypotensive effect of metoprolol

Parasympathomimetics: Concurrent use of parasympathomimetics may result prolonged bradycardia.

Sympathomimetics Metoprolol will antagonize the β1 effect of sympathomimetic agent but should have little influence on the bronchodilator effects of β2 agonists at normal therapeutic dose.

General anaesthetics an increase in the cardio-depressive effect due to the concomitant administration of inhalational anaesthetics is possible; however, since beta blockade can prevent excessive fluctuations in blood pressure whilst the patient is intubated and is rapidly antagonised with beta sympathomimetics, concomitant use is not contraindicated (see section 4.4).

Insulin and oral antidiabetic agents the blood glucose-reducing effect of insulin and oral blood glucose-reducing drugs can be intensified by beta blockers, in particular non-selective beta blockers. In this case, the dosage of the oral blood glucose-reducing drug must be adjusted.

Alpha blockers such as prazosine, tamsulosin, terazosine, doxazosine Increased risk of hypotension, especially severe orthostatic hypotension.

Floctafenine: Beta blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Skeletal muscle relaxant Curare muscle relaxant with metoprolol enhanced neuromuscular blockade. Blood pressure should be monitored and dosage adjustment of the antihypertensive be made if necessary.

Lidocaine Metoprolol can reduce the clearance of lidocaine.

Hepatic enzyme inducers Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol.

Mefloquine Increased risk of bradycardia

Antacid An increase in the plasma concentrations of metoprolol has been observed when the drug was coadministered with an antacid.

Alcohol During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly.

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive. Care should be taken when combining with other antihypertensive drugs or drugs that might reduce blood pressure, such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefits to improve control of hypertension.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Telmisartan

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.

Pregnancy
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 skeletaldeformations. 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.

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.

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 in reported 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.

Chlorthalidone

Renal Impairment
Chlorthalidone may precipitate azotemia.

Hepatic Impairment
Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Metoprolol

Pregnancy:
Since there are no well-controlled studies of the use of metoprolol in pregnant women, metoprolol may only be used during pregnancy if the benefits to the mother outweigh the risk to the embryo/foetus.
Beta blockers reduce placental perfusion and may cause foetal death and premature birth. Intrauterine growth retardation has been observed after long term treatment of pregnant women with mild to moderate hypertension. Beta blockers have been reported to cause prolonged delivery and bradycardia in the foetus and the new-born child. There are also reports of hypoglycaemia, hypotension, increased bilirubinaemia and inhibited response to anoxia in newborn children. Therefore the lowest possible dose should be used, and treatment should be discontinued 48-72 hours before the calculated birth date. If this is not possible, the newborn child should be monitored for 48-72 hours post-partum for signs and symptoms of beta blocking (e.g. cardiac and pulmonary complications).
Beta blockers have not shown potential teratogenic activity in animals, but reduced blood flow in the umbilical cord, growth retardation, reduced ossification and increased numbers of foetal and post-natal deaths.

Breast-feeding:
The concentration of metoprolol in breast milk is approximately three times higher than the one in the mother's plasma. Even though the risk of adverse effects in the breastfeeding baby would appear to be low after administration of therapeutic doses of the medicinal product (except in individuals with poor metabolic capacity), breastfeeding babies should be monitored for signs of beta blocking.

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with Telmisartan & Chlorthalidone and may affect the ability to drive and use machines.

4.8 Undesirable effects

Telmisartan

Renal dysfunction upon use with Ramipril.

Clinical Trials Experience

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 ≥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 1 Adverse Events Occurring at an Incidence of ≥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 ≥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 ofadverse events was required in 2.8% of 1455 patients treated with Telmisartan tablets and 6.1% of 380 placebo patients in reported 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 reported 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; and 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.

Cardiovascular Risk Reduction
Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events wererecorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%).

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).
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including Telmisartan.

Chlorthalidone

The following adverse reactions have been observed with chlorthalidone but there is not enough systematic collection of data to support an estimate of their frequency.

Gastrointestinal System Reactions: anorexia, gastric irritation, gastrointestinal (GI) upset, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System Reactions: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic Reactions: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Dermatologic-Hypersensitivity Reactions: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).

Cardiovascular Reaction: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

Other Adverse Reactions: hyperglycemia, glycosuria, hyperuricemia, hypercholesterolemia, muscle spasm, weakness, restlessness and impotence.

Metoprolol

Metoprolol is well tolerated, and the undesirable effects are generally mild and reversible. The most commonly reported adverse reactions during treatment is fatigue. Gangrene (in patients with severe peripheral circulatory disorder), thrombocytopenia and agranulocytosis may occur very rarely (less than 1 case per 10,000 patients).The following undesirable effects have been reported during the course of clinical studies or have been reported after routine use. In many cases, a link with the use of metoprolol (tartrate) has not been firmly established.

	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)
Blood and lymphatic system disorders					Thrombocytopenia, leukopenia

Endocrine disorders				Deterioration of latent diabetes mellitus	
Metabolism and nutrition disorders			Weight gain		
Psychiatric disorders			Depression, concentration problems, drowsiness or insomnia, nightmares	Nervousness, anxiety	Forgetfulness or memory impairment, confusion, hallucinations, personality changes (e.g. mood changes)
Nervous system disorders		Dizziness, headache	Paresthesia		
Eye disorders				Visual disturbances, dry or irritated eyes, conjunctivitis	
Ear and labyrinth disorders					Tinnitus, hearing problems
Cardiac disorders		Bradycardia, balance disturbances (very rarely with associated syncope), palpitations	Temporary exacerbation of symptoms of heart failure, first-degree atrioventricular block, precordial pain	Functional heart symptoms, heart arrhythmia, conductivity disturbances	

Vascular disorders	Pronounced blood pressure drop and orthostatic hypotension, very rarely with syncope	Cold hands and feet			Necrosis in patients with severe peripheral vascular disorders prior to treatment, exacerbation of claudicatio intermittens or Raynaud's syndrome
Respiratory, thoracic and mediastinal disorders		Functional dyspnea	Bronchospasms	Rhinitis	
Gastrointestinal disorders		Nausea, abdominal pain, diarrhoea, constipation	Vomiting	Dryness of mouth	Taste disturbances
Hepatobiliary disorders				Abnormal LFT values	Hepatitis
Skin and subcutaneous tissue disorders			Rash (psoriasislike urticaria and dystrophic cutaneous lesions), increased perspiration	Hair loss	Light hypersensitivity reactions, exacerbation of psoriasis, new psoriasis manifestation, psoriasis-like dermatological changes
Musculoskeletal and connective tissue disorders			Muscle spasms		Arthralgia, muscle weakness
Reproductive system and				Impotence and other sexual	

breast disorders				dysfunctions, induratio penis plastica (Peyronie's syndrome)	
General disorders and administration site conditions	Fatigue.		Oedema		

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Telmisartan

Limited data are available related to over dosage in humans. The most likely manifestations of over dosage would be hypotension 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.

Chlorthalidone

Symptoms of acute over dosage include nausea, weakness, dizziness and disturbances of electrolyte balance. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

Metoprolol

Toxicity:

7.5 g to an adult resulted in a lethal intoxication. 100 mg to a 5-year-old did not result in any symptoms after gastric lavage. 450 mg to a 12-year-old and 1.4 g to an adult resulted in moderate intoxication. 2.5 g to an adult resulted in a serious intoxication and 7.5 g to an adult resulted in a very serious intoxication.

Symptoms:

An overdose of metoprolol may cause severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, asystole, QT-prolongation (isolated

cases), poor peripheral perfusion, bronchospasms, loss of consciousness (even coma), nausea, vomiting or cyanosis. Respiratory depression, apnea, fatigue, fine tremor, seizures, sweating, paraesthesias, possible oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia, renal effects, transient symptoms of myasthenia.
In certain cases, especially among children and adolescents, CNS-symptoms and respiratory depression may predominate.

The symptoms may be exacerbated by concomitant ingestion of alcohol, antihypertensive agents, chinidine or barbiturates.

The first signs of an overdose present within 20 minutes to 2 hours after taking the medicinal product. The effects of massive overdose may persist for several days, despite declining plasma concentrations.

Management:
Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate. Even apparently well patients who have taken a small overdose should be closely observed for signs of poisoning for at least 4 hours.
Active charcoal, gastric lavage if necessary. NOTE! Atropine (0.25-0.5 mg i.v. to adults, 10-20 micrograms/kg to children) should be administered prior to gastric lavage (due to the risk of vagal stimulation). Intubation and assisted ventilation should occur based on a very wide indication. Adequate volume substitution. Glucose infusion. ECG monitoring. Atropine sulphate may be administered (0.5 - 2.0 mg intravenously) for blocking the vagus nerve. This can be repeated.

In case of severe hypotension, bradycardia or in risk of heart failure, the patient could be given a beta-1 agonist (e.g. prenalterol or isoprenaline) intravenously at intervals of 2-5 minutes or as continuous infusion until achieving the desired effect. If a selective beta-1 agonist is unavailable, dopamine may be used.

If the desired effect is not achieved, another sympathomimetic agent may be used, e.g. dobutamine or noradrenaline.

The patient may also be given 1-10 mg glucagon. It may be necessary to use a pacemaker. A beta-2 agonist may be administered intravenously to prevent bronchospasms in the patient, the patients should be monitored for evidence of cardiac arrhythmias during and after administration of the bronchodilator.

Note:The doses required for managing overdoses are much higher than the therapeutic doses usually applied as the beta blocker has blocked the beta receptors.

Note:In case of cardiac arrest after overdosage with a beta-blocker, cardiopulmonary resuscitation during several hours may be required.

5. Pharmacological properties

5.1 Mechanism of Action

METOCARD-CHT is a fixed-dose combination of telmisartan, an orally active angiotensin II antagonist acting on the AT1 receptor subtype, chlorthalidone, a thiazide-like diuretic, and metoprolol succinate, is a beta1-selective (cardioselective) adrenoceptor blocking agent, thus,

these drugs target the separate mechanisms involved in blood pressure regulation and hence may provide additive blood pressure reduction.

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. Chlorthalidone act primarily on the distal renal tubule (early convoluted part), inhibiting Na^+ CL^- reabsorption (by antagonizing the Na^+ CL^- cotransporter) and promoting Ca^{++} reabsorption. Metoprolol is a beta-1 selective beta blocker.It has a relatively greater blocking effect on beta receptors, than on beta receptors which are chiefly involved in broncho and vasodilation.

5.2 Pharmacodynamic properties

Telmisartan

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. Telmisartan has much greater affinity (more than 3000-fold) for the AT1 receptor than for the AT2 receptor.
Telmisartan does not inhibit the angiotensin converting enzyme [ACE (kininase II)]; hence, it does not affect the response to bradykinin. 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.
Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after a 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).

Chlorthalidone

Chlorthalidone produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the distal convoluted tubule and connecting segment of the nephron (and perhaps the early cortical collecting tubule). The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect. Like the thiazide diuretics, chlorthalidone produces dose-related reductions in serum potassium levels, elevations in serum uric acid and blood glucose, and it can lead to decreased sodium and chloride levels. The diuretic effect of chlorthalidone occurs in approximately 2.6 hours and continues for up to 72 hours.

Metoprolol

Metoprolol is a beta-1 selective beta blocker. It has a relatively greater blocking effect on beta receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release

of the fatty acids from fat stores) than on beta receptors which are chiefly involved in broncho and vasodilation. Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect. Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart. Metoprolol reduces tachycardia, decreases the cardiac output and the contractility, and lowers the blood pressure.

If required, metoprolol may be administered concomitantly with a beta-2 agonist to patients with symptoms of obstructive pulmonary disease.

5.3 Pharmacokinetic properties

Absorption and distribution

Telmisartan

Following oral administration, peak concentrations of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration time curve 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 mg and 160 mg, the bioavailability was 42% and 58%, respectively.
The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range of 20-160 mg, with greater than proportional increases of plasma concentrations 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 1.5-2.0 upon repeated once daily dosing.

Telmisartan is highly bound to plasma proteins (more than 99.5%), mainly albumin and alpha1-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.

Chlorthalidone

Following oral administration, peak plasma concentrations of chlorthalidone is reached at 1 hour. In whole blood, chlorthalidone is predominantly bound to erythrocyte carbonic anhydrase. In the plasma, approximately 75% of chlorthalidone is bound to plasma proteins, 58% of the drug being bound to albumin.

Metoprolol

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

Metabolism and Elimination

Telmisartan

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (more than 97%) was eliminated unchanged in the 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 acylglucuronide; 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 more than 800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Chlorthalidone

The mean plasma half-life of chlorthalidone is about 40 to 60 hours.
The major portion of the drug is excreted unchanged by the kidneys. Nonrenal routes of elimination have yet to be clarified. Data are not available regarding percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood-brain barrier.

Metoprolol

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 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. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardioselectivity. (See PRECAUTIONS, Drug Interactions.)

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of metoprolol succinate extended-release tablet 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 succinate extended-release tablet 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 succinate extended-release tablet, 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, ß1- 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 metoprolol succinate extended-release tablet administration.

Special Populations

Telmisartan

Pediatric: The pharmacokinetics of telmisartan has not been investigated in patients less than 18 years of age.

Geriatric: The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years

Gender: Plasma concentrations of telmisartan are generally 2-3 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.

Renal Impairment: Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.

Hepatic Impairment: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic impairment can be expected to have reduced clearance. In patients with hepatic impairment, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%**.**

Chlorthalidone

Renal Impairment

Renal dysfunction does not alter the pharmacokinetics of chlorthalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

Geriatrics

In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

Paediatrics

The safety and efficacy in children have not been established.

Metoprolol

Elderly patients

There are no adequate data from the use in patients above the age of 80. Take special precautions when increasing the dose. However, caution is advised in elderly patients as a fall in blood pressure or excessive bradycardia may have more pronounced effects.

Paediatric population:

There is limited data on the use of metoprolol in children and adolescents, therefore the use of Metoprolol is not recommended.

6. Nonclinical properties

6.1 Animal Toxicology or pharmacology

Telmisartan

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).

Chlorthalidone

There is no clinically relevant preclinical safety data available.

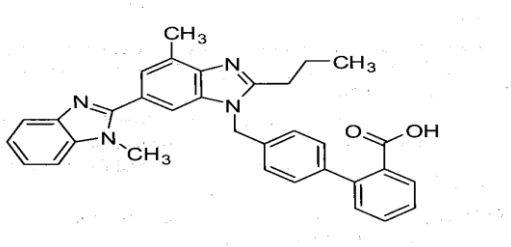
Metoprolol

There are no other relevant preclinical data than those already mentioned in other sections of this summary of product characteristics.

7. Description

Telmisartan

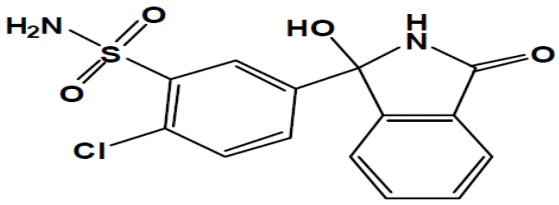
Telmisartan is 4'-{[4-mrthy-6-(1-methy-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl}-2-biphenyl-carboxylic acid having molecular formula of $C_{33}H_{30}N_4O_2$ and molecular weight is 514.6. The chemical structure is:



Telmisartan is a white to off-white crystalline powder, sparingly soluble in methylene chloride; slightly soluble in methanol; practically insoluble in water.

Chlorthalidone

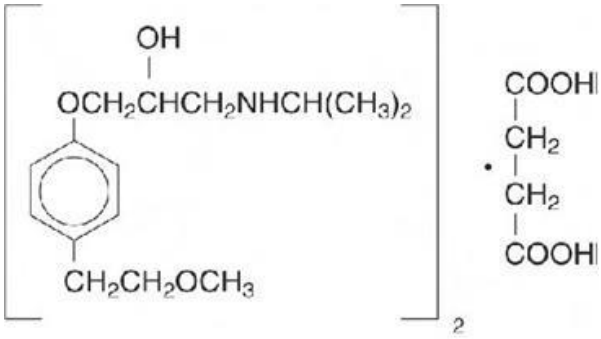
Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



Chlorthalidone is a white to yellowish-white, crystalline powder which is soluble in methanol; slightly soluble in ethanol (95%); practically insoluble in water, in ether and in chloroform.

Metoprolol

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. Its chemical name is (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt) having molecular weight of 652.81. Its empirical formula is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ with structural formula of



METOCARD-CHT 25

Telmisartan, Chlorthalidone and Metoprolol ER Tablets are white/yellow coloured, round shaped, biconvex film coated bilayered tablet having both sides plain.

METOCARD-CHT 50

Telmisartan, Chlorthalidone and Metoprolol ER Tablets are white/yellow coloured, capsule shaped, biconvex film coated bilayered tablet having scored on one side.

The excipients used are Dibasic Calcium phosphate, Methocel K100 Premium CR, Titanium dioxide, Acrypol 971-P, Isopropyl Alcohol, Purified Water, Talc Powder, Magnesium Stearate, Carbopol 71G, Meglumine, Microcrystalline Cellulose, Croscarmellose Sodium, Quinoline Yellow Lake, Sodium Hydroxide Pellets, Methylene Chloride, Crospovidone (XL10), Instacoat Transparent (ICS-329).

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

METOCARD-CHT is packed in blister strip of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30ºC and Protected from light and moisture.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• Dosage will be as directed by the Physician

• Keep all medicines out of reach of children

• If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you only.

Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What METOCARD-CHT is and what it is used for

Telmisartan, Chlorthalidone and Metoprolol used in the treatment of essential hypertension with stable coronary artery disease.

METOCARD-CHT is indicated for the treatment of essential hypertension with stable coronary artery disease.

9.2 What you need to know before you take METOCARD-CHT

Do not take METOCARD-CHT

- If you are allergic to Telmisartan, Chlorthalidone and Metoprolol or any of the other ingredients of this medicine.

Warnings and precautions

- Talk to your doctor before taking METOCARD-CHT
- When pregnancy is detected, discontinue Telmisartan as soon as possible. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and

death. Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia.

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.

- 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.

Infants

- Safety and efficacy in infants less than 2 months of age have not been established.

Other medicines and METOCARD-CHT

- Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Pregnancy and breast-feeding

- If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines

- Dizziness has been reported during treatment with Telmisartan, Chlorthalidone and Metoprolol and may affect the ability to drive and use machines.

9.3 How to take METOCARD-CHT

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

METOCARD-CHT Tablets should be swallowed with water.

Do not crush or chew.

If you take more METOCARD-CHT than you should contact your doctor if you took more tablets than you should. Your doctor will establish the best possible treatment of overdose.

The possible side effects of an overdose of METOCARD-CHT are nausea, weakness, dizziness, disturbances of electrolyte balance, hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

If you forget to take METOCARD-CHT:

Contact your doctor if you have missed one or more doses.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking METOCARD-CHT

Should your doctor decide to stop your METOCARD-CHT treatment, he/she will instruct you about the gradual withdrawal of METOCARD-CHT.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- gastrointestinal disturbances, nausea, vomiting, or diarrhoea
- muscle Pain
- Dizziness, insomnia, somnolence, anxiety, nervousness, paraesthesia, vertigo.
- asthma, cough, epistaxis, rhinitis, bronchitis, dyspnoea, sinusitis
- urticaria, rash, pruritus non-application site, dermatitis, , drug eruption, photosensitivity, Lyell's syndrome (toxic epidermal necrolysis)
- Fungal infection, abscess, otitis media, Respiratory tract infection, urinary tract infection.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent pharma available at:
https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store METOCARD-CHT

Store at a temperature not exceeding 30^{o}C and protected from light and moisture.

Keep out of reach of children.

9.6 Contents of the pack and other information

What METOCARD-CHT contains
The active substance is Telmisartan, Chlorthalidone and Metoprolol.

METOCARD-CHT 25
Telmisartan 40mg, Chlorthalidone 12.5 mg and Metoprolol Tartrate 25 mg

The excipients used are Dibasic Calcium phosphate, Methocel K100 Premium CR, Titanium dioxide, Acrypol 971-P, Isopropyl Alcohol, Purified Water, Talc Powder, Magnesium Stearate, Carbopol 71G, Meglumine, Microcrystalline Cellulose, Croscarmellose Sodium, Quinoline Yellow Lake, Sodium Hydroxide Pellets, Methylene Chloride, Crospovidone (XL10), Instacoat Transparent (ICS-329).

METOCARD-CHT 50
Telmisartan 40mg, Chlorthalidone 12.5 mg and Metoprolol Tartrate 50 mg

The excipients used are Dibasic Calcium phosphate, Methocel K100 Premium CR, Titanium dioxide, Acrypol 971-P, Isopropyl Alcohol, Purified Water, Talc Powder, Magnesium

Stearate, Carbopol 71G, Meglumine, Microcrystalline Cellulose, Croscarmellose Sodium, Quinoline Yellow Lake, Sodium Hydroxide Pellets, Methylene Chloride, Crospovidone (XL10), Instacoat Transparent (ICS-329).

METOCARD-CHT is packed in blister strip of 10 Tablets

10. Details of manufacturer

Manufactured in India by:

M/s Ravenbhel Healthcare Pvt Ltd.

At: EPIP, SIDCO, Kartholi, Bari-Brahmana, Jammu.

11. Details of permission or licence number with date

Mfg Lic No JK/01/17-18/LL/251 issued on 28.09.2021

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/METOCARD-CHT 25, 50 mg/MAY-22/01/PI