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

TELSAR CH

1. **Generic Name**

   Chlorthalidone and Telmisartan Tablets

2. **Qualitative and quantitative composition**

   TELSAR CH 40/6.25

   Each film coated tablet contains:

   Chlorthalidone I.P. ……..……6.25 mg

   Telmisartan I.P. …….....40 mg

   Excipients…….q.s.

   Colour: Titanium Dioxide I.P.

   The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000 and Castor Oil.

   TELSAR CH 40/12.5

   Each film coated tablet contains:

   Chlorthalidone I.P. ……..……12.5 mg

   Telmisartan I.P. …….....40 mg

   Excipients…….q.s.

   Colour: Ferric Oxide Yellow NF and Titanium Dioxide IP.

   The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

   TELSAR CH 80/12.5

   Each film coated tablet contains:

   Chlorthalidone I.P. ……..……12.5 mg

   Telmisartan I.P. …….....80 mg

   Excipients…….q.s.

Colour: Ferric Oxide Yellow NF and Titanium Dioxide IP.

The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

3. Dosage form and strength

Dosage Form: Film coated tablets

Strength: 40-6.25/12.5 mg & 80-12.5 mg

4. Clinical particulars

4.1 Therapeutic indication

TELSAR CH is indicated for the treatment of hypertension, to lower blood pressure:

- In patients not adequately controlled with monotherapy
- As initial therapy in patients likely to need multiple drugs to help achieve blood pressure goals

4.2 Posology and method of administration

The usual initial dosage is one tablet of TELSAR CH 40 mg orally once daily. The dose may be increased to two tablets of TELSAR CH 40 or TELSAR CH 80 once 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

TELSAR CH is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, chlorthalidone, 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 TELSAR CH 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.

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 (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.

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 80 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.

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 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.

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 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; 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.

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:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

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.

Chlorothalidone

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.

5. Pharmacological properties

5.1 Mechanism of Action

TELSAR CH is a fixed-dose combination of telmisartan, an orally active angiotensin II antagonist acting on the AT1 receptor subtype, and chlorthalidone, a thiazide-like diuretic. Thus, the two drugs target two 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.

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.

5.3 Pharmacokinetic properties

Absorption
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.

Chlorthalidone
Following oral administration, peak plasma concentrations of chlorthalidone is reached at 1 hour.

Distribution
Telmisartan
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
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.

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.

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.

6. Nonclinical properties

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

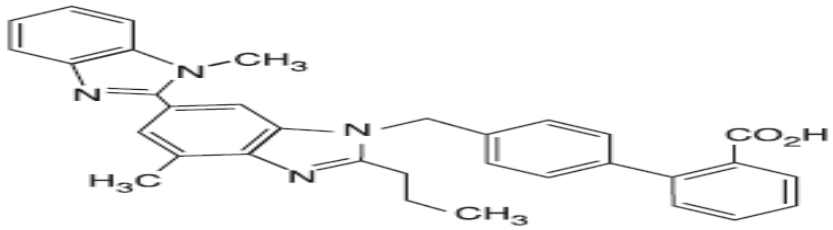
There is no clinically relevant preclinical safety data available.

7. Description

TELSAR CH is a fixed-dose combination of telmisartan, an orally active angiotensin II antagonist acting on the AT1 receptor subtype, and chlorthalidone, a thiazide-like diuretic. Thus, the two drugs target two separate mechanisms involved in blood pressure regulation and hence may provide additive blood pressure reduction.

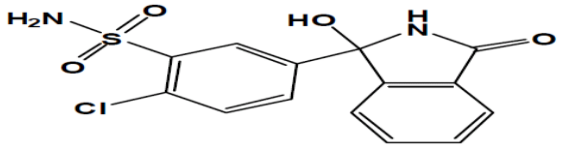
Telmisartan

Telmisartan, a nonpeptide molecule, 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. It has empirical formula $C_{33}H_{30}N_4O_2$ and molecular weight is 514.6. The chemical structure of Telmisartan is:



Chlorthalidone

Chlorthalidone is chemically described as 2-chloro-5(1-hydroxy-3-oxo-1- isoindolinyl) benzenesulfonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$. The structural formula is:



TELSAR CH 40/6.25

Chlorthalidone and Telmisartan Tablets are a white circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000 and Castor Oil.

TELSAR CH 40/12.5

Chlorthalidone and Telmisartan Tablets are a pale yellow coloured circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

TELSAR CH 80/12.5

Chlorthalidone and Telmisartan Tablets are a pale yellow coloured circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

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

TELSAR CH is available in strip of 10 tablets

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light and moisture

Keep all medicines out of reach of children.

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 TELSAR CH is and what it is used for

Telmisartan and Chlorthalidone is an antihypertensive medicine (a medicine used to treat blood pressure).

TELSAR CH is indicated for the treatment of hypertension, to lower blood pressure:

- In patients not adequately controlled with monotherapy
- As initial therapy in patients likely to need multiple drugs to help achieve blood pressure goals.

9.2 What you need to know before you take TELSAR CH

Do not take TELSAR CH

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

Warnings and precautions

- Talk to your doctor before taking TELSAR CH
- 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 TELSAR CH

- 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 may affect the ability to drive and use machines.

9.3 How to take TELSAR CH

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.

TELSAR CH Tablets should be administered orally with food to enhance absorption.

If you take more TELSAR CH 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 TELSAR CH are nausea, weakness, dizziness, disturbances of electrolyte balance, hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

If you forget to take TELSAR CH:

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 TELSAR CH

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

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 or pharmacist. 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: http://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.

9.5 How **to store TELSAR CH**

Store in a cool and dry place. Protect from light and moisture

Keep all medicines out of reach of children

9.6 Contents of the pack and other information

What **TELSAR CH** contains
The active substance is Telmisartan and Chlorthalidone.

TELSAR CH 40/6.25
Chlorthalidone…6.25mg and Telmisartan….40mg

The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000 and Castor Oil.

TELSAR CH 40/12.5
Chlorthalidone…12.5mg and Telmisartan….40mg

The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

TELSAR CH 80/12.5
Chlorthalidone…12.5mg and Telmisartan….80mg

The excipients used are Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Starch, Sodium Starch Glycolate, Aerosil, Talc, Croscarmellose Sodium, Magnesium Stearate, HPMC E15, Methylene Chloride, Titanium Dioxide, PEG 6000, Castor Oil and Ferric Oxide Yellow.

TELSAR CH is available in strip of 10 Tablets

10. Details of manufacturer

Manufactured in India by:

GKM New Pharma

Spl. Type No. 5, 6, 7 & 8,

PIPDIC Electronic Park,

Thirubuvanai, Puducherry – 605107.

11. Details of permission or licence number with date

Mfg. Lic. No. 09 13 2634 issued on 15.06.2015

12. Date of revision

APR/2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TELSAR CH40/6.25, 40/12.5, 80/12.5 /APR-21/01/PI