For the use only of Registered Medical Practitioner

WARNING
FETAL TOXICITY

- **When pregnancy is detected, discontinue Telmisartan as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus**

1. Generic Name & Brand Name

Telmisartan, Cilnidipine & Chlorthalidone Tablets
Telpres® Trio 12.5

2. Qualitative and Quantitative Composition:

Each film coated tablet contains:
Telmisartan IP……40 mg
Cilnidipine IP…….10 mg
Chlorthalidone IP……12.5 mg
Colours: Ferric Oxide USP NF Red & Titanium Dioxide I.P.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Dosage must be individualized.

Initiate therapy with the lowest possible dose, and then titrate according to individual patient response.

The recommended oral dosage is 1 tablet once daily or as directed by the Physician.

It may be substituted for its individually titrated components for patients on cilnidipine, telmisartan and chlorthalidone. It may be used as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on agents from two of the following antihypertensive classes: diuretics, calcium channel blockers, and angiotensin receptor blockers at their maximally tolerated, labeled, or usual dose.

Method of Administration:

For oral use only.

The patients should be instructed to swallow the tablet whole with liquid and must not be split, chewed or crushed. To achieve the best possible results, take your dose at the same time(s) each day.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to any of the active substance(s) or to any of the excipients.

Cilnidipine is contraindicated in: Shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis), unstable angina (excluding Prinzmetal's angina), and severe hypotension, haemodynamically unstable heart failure after acute myocardial infarction.

Telmisartan is contraindicated in: Second and third trimester of pregnancy; biliary obstructive disorders; severe hepatic impairment. The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

Chlorthalidone is contraindicated in patients with anuria or hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

4.4 Special warnings and precautions for use

Warning: Fetal Toxicity

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

Cilnidipine

It is advisable for elderly patients to initiate therapy with small doses, and gradually decrease dose with careful symptom observation when drug withdrawing. Other drug is recommended when daily dose is decreased to 5mg. Drug withdraw should be directed by the physician. Hypotension, poor cardiac reserve, and heart failure. Sudden withdrawal may exacerbate angina.

Discontinue in patients who experience ischemic pain following administration. Caution should be exercised during Cilnidipine use in pregnancy and lactation.

Telmisartan

Pregnancy: Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II

receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment: Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension: There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation: When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

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

Diabetic patients treated with insulin or antidiabetics: In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia: The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Close-monitoring of serum potassium in at risk patients is recommended.

Ethnic differences: As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other: As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

When pregnancy is detected Telmisartan should be discontinued as soon as possible as it can cause injury and even death to the developing foetus when used during second and third trimester of pregnancy.

Chlorthalidone

Chlorthalidone should be used with caution in severe renal disease. In patients with renal disease, chlorthalidone or related drugs may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

Hypokalemia may develop with chlorthalidone as with any other diuretic, especially with brisk diuresis when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone. Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Calcium excretion is decreased by thiazide-like drugs. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in few patients on thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulceration have not been seen.

Information for Patients: Patients should inform their physician if they have: (1) had an allergic reaction to chlorthalidone or other diuretics or have asthma, (2) kidney disease, (3) liver disease, (4) gout, (5) systemic lupus erythematosus, or (6) been taking other drugs such as cortisone, digitalis, lithium carbonate, or drugs for diabetes.

Patients should be cautioned to contact their physician if they experience any of the following symptoms of potassium loss: excess thirst, tiredness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting, or increased heart rate or pulse.

Patients should also be cautioned that taking alcohol can increase the chance of dizziness occurring.

Laboratory Tests: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

4.5 Drug Interactions
Cilnidipine

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

Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, the median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended:

Potassium sparing diuretics or potassium supplements: Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium.

Lithium: Reversible increases in the serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products: NSAIDs (*i.e.* acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the

co-administration of angiotensin II receptor antagonists and agents that inhibit cyclooxygenase (COX) may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use:

Other antihypertensive agents: The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic use): Reduction of the antihypertensive effect.

Chlorthalidone

Chlorthalidone may add to or potentiate the action of other antihypertensive drugs.

Insulin requirements in diabetic patients may be increased, decreased or unchanged. Higher dosage of oral hypoglycemic agents may be required.

Chlorthalidone and related drugs may increase the responsiveness to tubocurarine.

Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

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

Drug/Laboratory Test Interactions: Chlorthalidone and related drugs may decrease serum protein bound iodine levels without signs of thyroid disturbance.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)
Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

Cilnidipine: There are no adequate studies of cilnidipine in pregnant women to inform whether there is a drug associated risk in pregnancy. However, caution should be exercised during cilnidipine use in pregnancy.

Telmisartan: There are no adequate data from the use of Telmisartan in pregnant women. Studies in animals have shown reproductive toxicity.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist's therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia).

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

Chlorthalidone: Available data over decades from observational studies and reports with chlorthalidone use in pregnant women have not identified a drug-associated risk of major birth defects or miscarriage. However, adverse fetal outcomes, including fetal or neonatal jaundice, thrombocytopenia, hypoglycemia, and electrolyte abnormalities have been reported following maternal use of thiazide diuretics (see Clinical Considerations). Chlorthalidone should not be used as first-line therapy to treat hypertension in pregnancy. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse

outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation

Cilnidipine: It is not known whether cilnidipine is distributed in human breast milk or not However, caution should be exercised during cilnidipine use in lactation.

Telmisartan: Because no information is available regarding the use of Telmisartan during breast-feeding, Telmisartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Chlorthalidone: Chlorthalidone is present in human milk. There is no information regarding the effects of chlorthalidone on the breastfed infant or the effects on milk production. Because of the potential for chlorthalidone accumulation which may lead to serious adverse reactions in the breastfed infant (such as jaundice, thrombocytopenia, hyperglycemia, electrolyte abnormalities), advise patients that breastfeeding is not recommended during treatment with chlorthalidone.

Paediatric use

Safety and effectiveness in children have not been established.

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.

Geriatric Use

Telmisartan: Of the total number of patients receiving telmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment of telmisartan is necessary for elderly patients.

Chlorthalidone: Clinical studies of Chlorthalidone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of telmisartan 20 mg is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

Telmisartan is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment; the posology should not exceed telmisartan 40 mg once daily. Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

4.7 Effects on ability to drive and use machines

There's no report of cilnidipine's effect on the ability to drive and use machines. However, cilnidipine can have minor or moderate influence on the ability to drive and use machines. If patients taking cilnidipine suffer from dizziness, headache or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan.

4.8 Undesirable effects

Cilnidipine

Dizziness; flushing; headache; hypotension; peripheral oedema; tachycardia; palpitations; GI disturbances; increased micturition frequency; lethargy; eye pain; depression; ischaemic chest pain; cerebral or myocardial ischaemia; transient blindness; rashes; fever; abnormal liver function; gingival hyperplasia; myalgia; tremor; impotence.

The mostly reported adverse reactions (mild and rare adverse reactions) during cilnidipine treatment are nausea, headaches, swelling, low blood pressure, and edema (water retention), dizziness, cardiopalmus, and puffiness, which can be tolerated by most patients, and no management should be taken.

Lab Interference: Falsely elevated spectrophotometric values of urinary vanillylmandelic acid.

Telmisartan

The following adverse reaction is described elsewhere in labeling: Renal dysfunction upon use with ramipril.

Clinical Trials Experience:

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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 as follows: Upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis.

In addition to these adverse events (above), 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 of adverse events was required in 2.8% of patients treated with telmisartan and 6.1% of patients treated with placebo, 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 echocardiography (ECG).

Central Nervous System: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.

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

Metabolic: gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: arthritis, arthralgia, leg cramps.

Psychiatric: anxiety, depression, nervousness.

Resistance Mechanism: infection, fungal infection, abscess, otitis media.

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

Skin: dermatitis, rash, eczema, pruritus.

Urinary: micturition frequency, cystitis.

Vascular: cerebrovascular disorder.

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

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

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

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.

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

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy because of abnormal hepatic function.

Post-marketing 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 are associated with chlorthalidone: Hypotension, impaired renal function, electrolyte abnormalities and metabolic disturbances. The following adverse reactions have been observed, but there is not enough systematic collection of data to support an estimate of their frequency.

Gastrointestinal System Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), and pancreatitis.

Central Nervous System Reactions: Dizziness, vertigo, paresthesias, headache, and xanthopsia.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, and 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, muscle spasm, weakness, restlessness, impotence.

Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

4.9 Overdose

Cilnidipine

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

Telmisartan

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

Chlorthalidone

Symptoms of acute overdosage 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

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.

Cilnidipine is a third generation dihydropyridine calcium antagonist with a slow onset and long duration of action. Calcium antagonists inhibit influx of extracellular calcium ions into the cells, resulting in decreased vascular smooth muscle tone and vasodilation, leading to a reduction in blood pressure.

Chlorthalidone is a long-acting oral diuretic with antihypertensive activity. The diuretic effects of chlorthalidone and the benzothiadiazine (thiazide) diuretics appear to arise from similar mechanisms and the maximal effect of chlorthalidone and the thiazides appear to be similar. The site of the action appears to be the distal convoluted tubule of the nephron. 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.

5.2 Pharmacodynamic Properties

<u>Cilnidipine</u>

Cilnidipine is a dihydropyridine calcium antagonist. Compared with other calcium antagonists, cilnidipine can act on the N-type calcium channel that existing sympathetic nerve end besides acting on L-type calcium channel that similar to most of the calcium antagonists. It acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of norepinephrine and suppressing the increase in stress blood pressure. It can be combined with the fluazifop sites in L-type calcium channel on vascular smooth muscle cellular membrane, and

inhibit the across membrane inflow of Ca2+ through L-type calcium channel, accordingly relax and expand vascular smooth muscles to reduce blood pressure.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterized AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse events. In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Chlorthalidone

Chlorthalidone is a long-acting oral diuretic with antihypertensive activity. Its diuretic action commences a mean of 2.6 hours after dosing and continues for up to 72 hours. The drug produces diuresis with increased excretion of sodium and chloride. The diuretic effects of chlorthalidone and the benzothiadiazine (thiazide) diuretics appear to arise from similar mechanisms and the maximal effect of chlorthalidone and the thiazides appear to be similar. The site of the action appears to be the distal convoluted tubule of the nephron. 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.

5.3 Pharmacokinetic properties

Cilnidipine

Cilnidipine presents a very rapid absorption with a maximum peaked concentration after 2 hours. Its distribution tends to be higher in the liver as well as in kidneys, plasma and other tissues. Cilnidipine does not present a high accumulation in the tissue after repeated oral administration. Drugs on the group of dihydropyridines such as cilnidipine tend to have a large volume of distribution. Cilnidipine presents a very high protein binding that represents to even 98% of the

administered dose. Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by a dehydrogenation process. The major enzymatic isoform involved in cilnidipine dehydrogenation of the dihydropyridine ring is CYP3A. Cilnidipine gets eliminated through the urine in a proportion of 20% of the administered dose and 80% is eliminated by the feces. The half-life of the hypotensive effect for cilnidipine is of about 20.4 min.

Telmisartan

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l. Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Telmisartan is characterized by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Chlorthalidone

Following oral administration, peak plasma concentrations of chlorthalidone is reached at 1 hour. 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. Chlorthalidone, presystemic metabolism is noted to be 0.5% ±0.5. 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. Major portion of the drug is excreted unchanged by the kidneys. Non-renal routes of elimination have yet to be clarified. The mean plasma half-life of chlorthalidone is about 40-60 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Cilnidipine

No relevant data available.

Telmisartan

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Developmental Toxicity

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day . In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about0.64 and 3.7 times, on a mg/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Chlorthalidone

No information is available.

7. Description

Telpres Trio 12.5 is supplied for oral administration, as film coated tablet of Telmisartan, Cilnidipine and Chlorthalidone. Each film coated tablet of Telpres Trio 12.5 contains Telmisartan 40 mg, Cilnidipine 10 mg and Chlorthalidone 12.5 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition and handling instructions

Refer Pack

9. Patient Counseling Information

Advise the patient to read this entire leaflet carefully before you are given this medicine because it contains important information for you. Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor or pharmacist or nurse. If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What Cilnidipine/Telmisartan/Chlorthalidone Tablets is and what it is used for?

This is a prescription medicine that contains Cilnidipine, Telmisartan and Chlorthalidone as active ingredient. It is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Your doctor has probably also recommended that you make some changes in your lifestyle to help lower your blood pressure (for example losing weight, giving up smoking, reducing the amount of alcohol you drink and reducing the amount of salt in your diet). Your doctor may also have urged you to take regular exercise, such as walking or swimming. It is important to follow this advice from your doctor.

Who should not take Cilnidipine/Telmisartan/Chlorthalidone Tablets?

You should not take Cilnidipine/Telmisartan/Chlorthalidone Tablets, if you are allergic or hypersensitive to the active ingredients cilnidipine, telmisartan and chlorthalidone) or any other of its components.

What is the most important information I should know about Cilnidipine/Telmisartan/Chlorthalidone Tablets?

Cilnidipine/Telmisartan/Chlorthalidone Tablets can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking Cilnidipine/Telmisartan/Chlorthalidone Tablets, tell your doctor right away.

What should I tell my doctor before taking Cilnidipine/Telmisartan/Chlorthalidone Tablets?

Before you take Cilnidipine/Telmisartan/Chlorthalidone Tablets, tells your doctor if you:

• are pregnant or are planning to become pregnant. See "What is the most important information I should know about Cilnidipine/Telmisartan/Chlorthalidone Tablets?"

• are breast-feeding or plan to breast-feed. Cilnidipine/Telmisartan/Chlorthalidone Tablets can pass into your breast milk and may harm your baby. You and your doctor should decide if you will take Cilnidipine/Telmisartan/Chlorthalidone tablets or breast-feed. You should not do both. Talk with your doctor about the best way to feed your baby if you take Cilnidipine/Telmisartan/Chlorthalidone Tablets.

• have liver problems.

• have kidney problems.

• have heart problems.

• have any other medical conditions.

Patients should inform their doctor if they have had an allergic reaction to chlorthalidone or other diuretics; kidney disease; gout; been taking lithium carbonate.

Patients should be cautioned to contact their physician if they experience any of the following symptoms of potassium loss: excess thirst, tiredness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting or increased heart rate or pulse.

Patients should inform their doctor if they have symptoms of light-headedness or dizziness.

Tell your doctor if you are taking any of the following medicines used to treat high blood pressure:

• An ACE-inhibitor (for example enalapril, lisinopril and ramipril), in particular if you have diabetes related kidney problems.

• Aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking telmisartan (Cilnidipine/Telmisartan/Chlorthalidone Tablets) before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of telmisartan. Cilnidipine/Telmisartan/Chlorthalidone tablet is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Inform female patients of childbearing age about the consequences of exposure to drugs that act on the renin-angiotensin system (telmisartan) during pregnancy. Discuss treatment options with women planning to become pregnant. Advise these patients to report pregnancies to their physicians as soon as possible.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Telmisartan is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment

for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely. Advise females not to breastfeed during treatment with chlorthalidone. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

You may feel sleepy or dizzy while being treated for your high blood pressure. If this happens, do not drive or use machines until the symptoms wear off. Ask your doctor for advice.

How should I take Cilnidipine/Telmisartan/Chlorthalidone Tablets?

Always take Cilnidipine/Telmisartan/Chlorthalidone Tablets exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Posology

Dosage must be individualized. Initiate therapy with the lowest possible dose, and then titrate according to individual patient response.

The recommended adult dosage is 1 tablet once daily or to be given as directed by the Physician. Your doctor will tell you how much Cilnidipine/Telmisartan/Chlorthalidone Tablets to take and when to take it. Your doctor may change your dose if needed.

Method of administration: For oral use only.

In order to assist compliance, it is recommended that Cilnidipine/Telmisartan/Chlorthalidone tablets be taken at about the same time each day. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet must not be split, chewed or crushed.

If you take more Cilnidipine/Telmisartan/Chlorthalidone tablets than you should: If you take more tablets than you should or if a child accidentally swallows some, go to your doctor or nearest emergency department immediately and take your medicine pack with you.

If you forget to take Cilnidipine/Telmisartan/Chlorthalidone tablets: If you forget a dose, take your normal dose on the following day as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Cilnidipine/Telmisartan/Chlorthalidone tablets: It is important to continue to take Cilnidipine/Telmisartan/Chlorthalidone tablets unless your doctor tells you to stop.

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

What are possible side effects of Cilnidipine/Telmisartan/Chlorthalidone Tablets?

Like all medicines, this medicine can cause side effects, although not everybody gets them. If they do occur, they are often mild and do not require treatment to be stopped.

Cilnidipine/Telmisartan/Chlorthalidone Tablets may cause serious side effects, including:

• Injury or death to your unborn baby. See "What is the most important information I should know about Cilnidipine/Telmisartan tablets?"

• Low blood pressure (hypotension) is most likely to happen if you also: take water pills (diuretics); are on a low salt diet; get dialysis treatments; have heart problems; get sick with vomiting or diarrhea. If you feel faint or dizzy, lie down and call your doctor right away.

The most common side effects of Cilnidipine/Telmisartan tablets include:

• swelling in your hands, ankles, or feet,
• Flushing or sudden redness of the face and neck,
• Dizziness,
• Back pain,
• Feeling tired or sleepy,
• Abdominal pain, nausea, or diarrhea,
• Low blood pressure or a sudden drop in blood pressure with fainting.

The following adverse reactions are associated with chlorthalidone: Hypotension, impaired renal function, electrolyte abnormalities and metabolic disturbances.

These are not all the possible side effects of Cilnidipine/Telmisartan/Chlorthalidone Tablets. Tell your doctor if you have any side effect that bothers you or that does not go away.

Reporting of side effects or suspected adverse reaction: If you get or experience any side effects, talk to your doctor or pharmacist and report it. You can also report side effects directly via the National Pharmacovigilance Program of India. By reporting side effects, you can help provide more information on the safety of this product.

How should I store Cilnidipine/Telmisartan/Chlorthalidone Tablets?

Keep all medicines out of the reach of children.

Do not store above 30˚C, to be protected light and moisture.

Do not use this medicine after the expiry date, which is stated on the carton and the container after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

General information about the safe and effective use of Cilnidipine/Telmisartan/Chlorthalidone Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Cilnidipine/Telmisartan/Chlorthalidone Tablets for a condition for which it was not prescribed. Do not give Cilnidipine/Telmisartan/Chlorthalidone Tablets to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider.

What are the ingredients in this medicine?

The active ingredients are: Cilnidipine, Telmisartan and Chlorthalidone.

Each film coated tablet contains: Cilnidipine IP 10 mg, Telmisartan IP 40 mg and Chlorthalidone IP 12.5 mg.

Any other information

Keep this medicine out of the sight and reach of children.

10. Details of manufacturer
Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 & 111 to 116
First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.
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11. Details of permission or licence number
Refer Pack for Permission/License details

12. Date of revision
Version 2.0, dated 30-Dec-25

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**