SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product:

TELMI TAB – 80 CT

Telmisartan 80 mg and Chlorthalidone 12.5 mg Tablets

2. Qualitative and Quantitative composition:

Composition:

Each uncoated tablet contains:

Telmisartan USP 80 mg

Chlorthalidone USP 12.5 mg

Excipients Q. S.

3. Pharmaceutical Form:

Tablet for Oral Administration.

White coloured, circular shaped, flat, uncoated tablets having breakline on one side and plain on other side.

4. Clinical Particulars:

4.1 Therapeutic Indications:

It is indicated for the treatment of essential 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

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily stroke and myocardial infarction.

4.2 Posology and method of administration:

Dosage must be individualized. The usual initial dosage is one tablet of Telmi tab-40CT taken orally once daily. A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 40 mg may be switched to Telmi tab-40CT. The dose may be increased, if necessary, to two tablets of Telmi tab-40CT or one tablet of Telmi tab-80CT daily.

A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg may be switched to two tablets of Telmi tab-40CT or one tablet of Telmi tab-80CT daily. A patient whose blood

pressure is not adequately controlled with chlorthalidone 25 mg once daily may be switched to Telmi tab-40CT once / twice daily or Telmi tab-80CT once daily. Patients controlled by 25 mg chlorthalidone but who experience dose-limiting adverse reaction (such as hypokalemia) may be switched to Telmi tab-40CT or Telmi tab-80CT once daily, which will reduce the dose of chlorthalidone without reducing the overall expected antihypertensive response. If blood pressure remains uncontrolled after 2-4 weeks of therapy, other anti-hypertensive agents may be added as required.

4.2 Contraindications:

- Hypersensitivity (e.g. anaphylaxis or angioedema) to telmisartan, chlorthalidone or any sulfonamide-derived drugs
- Hypertension during pregnancy
- Biliary obstructive disorders
- Severe hepatic or renal failure (creatinine clearance <30ml/min)
- Patients with anuria
- Refractory hypokalemia, hyponatremia and hypercalcemia
- Symptomatic hyperuricemia (history of gout or uric acid calculi)
- Untreated Addison's disease

4.4 Special warning and precaution for use:

Hypotension in volume and/or Salt- Depleted Patients

In patients with an activated renin angiotensin system (RAS), such as volume-or salt-depleted patients, symptomatic hypotension may occur after initiation of therapy. This condition should either be corrected prior to administration of Telmi tab CT, or treatment should be started under close medical supervision with a reduced dose.

Serum Electrolyte Imbalances

Telmisartan

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.

Chlorthalidone

As with all other thiazide-type diuretics, chlorthalidone has been associated with electrolyte disturbances such as hypokalemia, hypomagnesaemia, hyperglycemia and hyponatremia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided

4.5 Interaction with other medicinal products and other forms of interaction:

The pharmacokinetics of telmisartan and chlorthalidone are not altered when the drugs are co-administered.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure.

Concomitant administration of certain NSAIDs (e.g. indomethacin) may reduce the diuretic and antihypertensive activity of chlorthalidone.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ARBs including telmisartan.

Digoxin

When telmisartan is co-administered with digoxin, it will increase the level or effect of telmisartan.

Aliskiren

Aliskiren should not be co-administered with Telmi tab CT in patients with diabetes (due to telmisartan component). Use of aliskiren with Telmi tab CT should also be avoided in patients with renal impairment (GFR <60 ml/min).

Chlorthalidone

Anti-diabetic Agents

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents since chlorthalidone, like other thiazide-type diuretics, may affect blood glucose levels.

Anticholinergic Agents

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Calcium Salts and Vitamin D

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics.

Others

Diuretics potentiate the action antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycemic effect of diazoxide and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

4.6 Fertility, Pregnancy and Lactation:

Telmisartan

Use of drugs that act on the RAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios (deficiency of amniotic fluid) can be associated with fetal lung hypoplasia (abnormal deficiency of cells or structural elements) and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death.

Chlorthalidone

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolemia, increased blood viscosity and reduced placental perfusion. There have been reports of fetal bone marrow depression, thrombocytopenia, and fetal and neonatal jaundice associated with the use of thiazide diuretics.

Lactation: It is not known whether telmisartan is excreted in human milk. Chlorthalidone passes into the breast milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue Telmi tab CT, taking into account the importance of the drugs to the mother.

4.7 Effects on the ability to drive and use machines:

Not available

4.8 Undesirable effects:

Telmisartan

Adverse events experienced with telmisartan have generally been mild and transient in nature are as follows: Upper respiratory tract infection, back pain, sinusitis, diarrhoea and pharyngitis, have infrequently required discontinuation of therapy.

Other Symptoms: Influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral oedema.

Chlorthalidone:

Electrolytes and Metabolic Disorders (mainly at higher doses): hypokalemia, hyperuricemia, rise in blood lipids, hyponatremia, hypomagnesemia and hyperglycemia

Skin: urticaria and other forms of skin rash

Cardiovascular System: postural hypotension

Central nervous System: paraesthesia, headache.

Gastro-intestinal Tract: mild nausea and vomiting, gastric pain, constipation and diarrhoea

Blood: thrombocytopenia, leukopenia, agranulocytosis and eosinophilia

Other: idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

4.9 Overdose:

Telmisartan: The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Chlorthalidone: Symptoms of acute overdosage include nausea, weakness, dizziness and disturbances of electrolyte balance.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin receptor blocker

Telmisartan: ATC code: C09CA07

Chlorthalidone: ATC code: C03BA04

Mechanism of action

The combination of telmisartan and chlorthalidone has been shown to be effective in lowering blood pressure. Both telmisartan and chlorthalidone lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

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 angiotensin II type 2 (AT2) receptor.

Telmisartan does not inhibit the angiotensin converting enzyme; 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.

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.

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 alpha-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 ^{14}C-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. Non-renal 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

Paediatric

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. The elimination of chlorthalidone in elderly patients 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.

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. Renal dysfunction does not alter the pharmacokinetics of chlorthalidone as well, 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. 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 for either, telmisartan or chlorthalidone 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%.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

6.2 Incompatibilities:

Not applicable.

6.3 Shelf Life:

36 months.

6.4 Special Precautions for storage:

Store at temperature not exceeding 30°C.

6.5 Nature and contents of container:

Blister pack of 3 x 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

8. Marketing Authorization Number:

9. Date of first Authorization /renewal of the authorization:

10. Date of revision of text:

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