Summary of Product Characteristics (SmPC)

1. **Name of the Finished Pharmaceutical Product: TELDURET 80/25mg**
   Generic Name: Telmisartan & Hydrochlorothiazide Tablets USP

2. **Quality and Quantitative Composition**

2.1 Qualitative Composition

Composition:

Each uncoated bilayered tablet contains:

Telmisartan	USP	80mg
Hydrochlorothiazide	USP	25mg
Excipients		q.s

Colour: Tartrazine Lake
(In Hydrochlorothiazide Layer)

2.2 Quantitative Composition

S.No.	Ingredients	Claim	Specification	Quantity Per tablet (mg or ml)	Quantity Per Tablet (in %)	Function
LAYER-1 (WHITE PART)						
Active:						
1	Telmisartan*	80.0mg	USP	080.000mg	029.630	API
Tablet Core:						
2	Mannitol	-------	BP	112.000mg	041.481	Diluent
3	Meglumine	-------	BP	027.500mg	010.190	Diluent
4	Potassium Hydroxide	-------	BP	020.000mg	007.407	Buffering agennt
5	Dichloromethane**	-------	BP	000.060ml	--------	Solvent
6	Purified Water**	-------	BP	000.040ml	--------	Solvent
7	Purified Talc	-------	BP	004.500mg	001.666	Glidant
8	Magnesium Stearate	-------	BP	005.000mg	001.851	Lubricant
9	Sodium Starch Glycolate (Type-A) 1	-------	BP	008.000mg	002.962	Disintegrant
10	Colloidal anhydrous silica	-------	BP	005.000mg	001.851	Anti-adherent
11	Kyron-T 314	-------	IH	008.000mg	002.962	Disintegrant
			Total	**270.00mg**	**100.00**	-------
LAYER-2 (COLOUR PART)						
Active:						
1.	Hydrochlorothiazide*	25.0mg	USP	025.000mg	019.230	API
Tablet Core:						
2.	Lactose monohydrate	--------	BP	050.000mg	038.462	Diluent
3.	Maize Starch	--------	BP	015.800mg	012.154	Diluent
4.	Microcrystalline Cellulose	--------	BP	021.800mg	016.769	Diluent

5.	Colour: Tartrazine Lake	--------	IH	000.600mg	000.462	Colourant
6.	Povidone (K-30)	--------	BP	002.500mg	001.923	Binder
7.	Isopropyl Alcohol**	--------	BP	000.060ml	--------	Solvent
8.	Purified Talc	--------	BP	002.500mg	001.923	Glidant
9.	Magnesium Stearate	--------	BP	002.000mg	001.538	Lubricant
10.	Croscarmellose Sodium	--------	BP	004.000mg	003.077	Disintegrant
11.	Colloidal anhydrous silica	--------	BP	000.600mg	000.462	Anti-adherent
12.	Microcrystalline Cellulose-102	--------	BP	005.200mg	004.000	Diluent
			Total	**130.00mg**	**100.00**	-------

Average Weight of Tablet: 400.00mg±3.00%/Tablet(White 270.00mg + Colour 130.00mg)
* Material calculated on 100% assay basis.
** Will not remain in the final product.

Abbreviation-USP-United states pharmacopoeia, **BP**-British Pharmacopoeia, **mg**-Milligram **%**-Percentage, **IH**-In-House, **ml**-Milliliter, **Q.S**-quantity sufficient**, Qty.:** Quantity, **Tab.:** Tablet, **Spec.:** Specification, **API:** Active Pharmaceutical Ingredient.

3. Pharmaceutical Form

Oral Solid Dosage Form (Uncoated Tablet)

4. Clinical Particulars

4.1 Therapeutic indications

Hypertension

Telmisartan/hydrochlorothiazide is indicated for the treatment of hypertension.

4.2 Posology and method of administration

The usual starting dose of telmisartan is 40 mg once a day; blood pressure response is dose related over the range of 20-80 mg. Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision, Hypotension in Volume Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision. Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects of telmisartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the

latter. Therapy with any combination of telmisartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Telmisartan/hydrochlorothiazide tablets may be administered with other antihypertensive agents.

Telmisartan/hydrochlorothiazide tablets may be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components. Dose Titration by Clinical Effect

Telmisartan/hydrochlorothiazide tablets are available as tablets containing either telmisartan 40 mg and hydrochlorothiazide 12.5 mg, or telmisartan 80 mg and hydrochlorothiazide 12.5 mg or 25 mg. A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg (see above) may be switched to telmisartan/hydrochlorothiazide tablets, telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide may be switched to telmisartan 80 mg/hydrochlorothiazide 12.5 mg or telmisartan 80 mg/hydrochlorothiazide 25 mg tablets once daily. The clinical response to telmisartan/hydrochlorothiazide tablets should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to 160/25 mg, if necessary. Those patients controlled by 25 mg hydrochlorothiazide but who experience hypokalemia with this regimen, may be switched to telmisartan 80 mg/hydrochlorothiazide 12.5 mg tablets once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response.

Patients with Renal Impairment

The usual regimens of therapy with telmisartan/hydrochlorothiazide tablets may be followed as long as the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so telmisartan/hydrochlorothiazide tablets are not recommended.

Patients with Hepatic Impairment

Telmisartan/hydrochlorothiazide tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination.

4.3 Contraindications

Telmisartan/hydrochlorothiazide is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Do not co-administer aliskiren with telmisartan/hydrochlorothiazide in patients with diabetes.

4.4 Special Warnings and Precautions for Use

Fetal Toxicity

Pregnancy Category

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/hydrochlorothiazide 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 reninangiotensin 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/hydrochlorothiazide, 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/hydrochlorothiazide for hypotension, oliguria, and hyperkalemia.

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume-Depleted Patients

Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of Telmisartan HCT (telmisartan and hydrochlorothiazide) tablets. Treatment should be In controlled trials using the telmisartan/hydrochlorothiazide

combination treatment, no patient administered 40/12.5 mg, 80/12.5 mg or 80/25 mg had a decrease in potassium ≥1.4 mEq/L, and no patient experienced hyperkalemia. No discontinuations due to hypokalemia occurred during treatment with the telmisartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

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 lifethreatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated 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), treatment with angiotensin-converting enzyme 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 may be anticipated in patients

treated 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 an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Telmisartan

Digoxin: When telmisartan was coadministered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma

Concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs: Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide 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.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal

clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with telmisartan/hydrochlorothiazide.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassiumsparing and thiazide diuretics. Therefore, when telmisartan/hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

4.6 Fertility, pregnancy and lactation

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.

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

Breast-feeding

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

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Telmisartan/Hydrochlorothiazide during breast feeding is not recommended. If Telmisartan/Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

Fertility

In preclinical studies, no effects of telmisartan and hydrochlorothiazide on male and female fertility were observed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥ 1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4% vs 43.9 %) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term.

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention:

very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Uncommon: Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis
Rare: Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders
Uncommon: Anaemia
Rare: Eosinophilia, thrombocytopenia
Immune system disorders
Rare: Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders
Uncommon: Hyperkalaemia
Rare: Hypoglycaemia (in diabetic patients)
Psychiatric disorders
Uncommon: Insomnia, depression
Rare: Anxiety
Nervous system disorders
Uncommon: Syncope
Rare: Somnolence
Eye disorders
Rare: Visual disturbance
Ear and labyrinth disorders
Uncommon: Vertigo
Cardiac disorders
Uncommon: Bradycardia
Rare: Tachycardia
Vascular disorders
Uncommon: Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough

Very rare:	Interstitial lung disease[4]
Gastrointestinal disorders	
Uncommon:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
Rare:	Dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders	
Rare:	Hepatic function abnormal/liver disorder[3]
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, hyperhidrosis, rash
Rare:	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders	
Uncommon:	Back pain (e.g. sciatica), muscle spasms, myalgia
Rare:	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	
Uncommon:	Renal impairment including acute renal failure
General disorders and administration site conditions	
Uncommon:	Chest pain, asthenia (weakness)
Rare:	Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

Description of selected adverse reactions

Sepsis

In the profess trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established

4.9 Overdose

Telmisartan

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

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Telmisartan/hydrochlorothiazide is a combination of telmisartan, an orally active angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Mechanism of action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 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.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on rennin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

5.2 Pharmacokinetic properties

Absorption

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 – 1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42 % and 58 %, respectively. Food slightly reduces the bioavailability of telmisartan with a reduction in the area under the plasma concentration time curve (AUC) of about 6 % with the 40 mg tablet and about 19 % after a 160 mg dose. By 3 hours after administration plasma

concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of Telmisartan peak concentrations of hydrochlorothiazide are reached in approximately 1.0 – 3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60 %.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5 %) mainly albumin and alpha l- acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 l/kg.

5.3 Preclinical safety data

No additional preclinical studies have been performed with the Fixed Dose Combination product 80 mg/25 mg. Previous preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, in doses producing exposure comparable to that in the clinical therapeutic range, caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

Toxicological findings also well known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed.

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol
Meglumine
Potassium Hydroxide
Dichloromethane
Purified Water
Purified Talc
Magnesium Stearate
Sodium Starch Glycolate
(Type-A) 1
Colloidal anhydrous silica
Kyron-T 314
Lactose monohydrate
Maize Starch
Microcrystalline Cellulose
Col. Tartrazine Lake
Povidone (K-30)
Isopropyl Alcohol
Croscarmellose Sodium
Microcrystalline Cellulose-102

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C.Protect from light & moisture.

6.5 Nature and contents of container

3 x10 Tablets Packed in printed aluminum foils and base foil.

6.6 Special precautions for disposal

No special requirements.

7. Marketing Authorisation Holder

Marketed by:
Biogenerics Nigeria Limited
13 Hughes Avenue,Alagomeji
Yaba lagos,Lagos Nigeria
www.biogenericsltd.com

Manufactured by:
PSYCHOTROPICS INDIA LIMITED

Plot No. 46 & 49, Sector- 6A,
IIE, SIIDCUL, Haridwar–249403,
(Uttarakhand) INDIA
www.psychoindia.com

8. Marketing Authorisation Numbers

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9. Date Of First Authorisation/Renewal Of The Authorisation

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10. Date Of Revision Of The Text
