SUMMARY OF PRODUCT CHARACTERISTICS

VISOTEL TABLETS
(TELMISARTAN & HYDROCHLOROTHIAZIDE TABLETS USP)

1. NAME OF THE MEDICINAL PRODUCT:

VISOTEL
TELMISARTAN & HYDROCHLOROTHIAZIDE TABLETS USP

COMPOSITION:
Each film coated tablet contains:
Telmisartan USP 40 mg
Hydrochlorothiazide USP 12.5 mg
Excipients q.s.
Colour: Titanium Dioxide

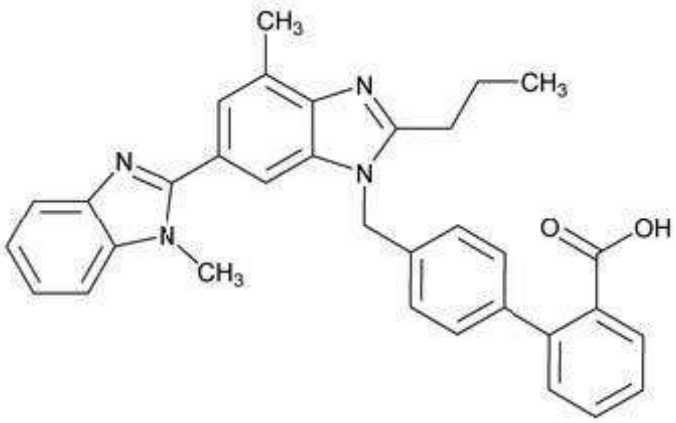
2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

CHEMICAL NAME AND THE STRUCTURAL FORMULA OF EACH ACTIVE INGREDIENT:-

TELMISARTAN

Chemical Name:
2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid

Chemical Structure:



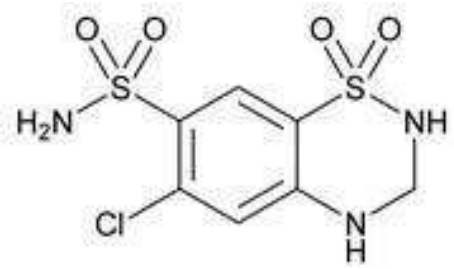
MOLECULAR FORMULA- $C_{33}H_{30}N_4O_2$

MOLECULAR WEIGHT- 514.62 g/mol

HYDROCHLOROTHIAZIDE

Chemical Name:
6-chloro-1,1-dioxo-3,4-dihydro-2H-1$l^{6},2,4-benzothiadiazine-7-sulfonamide

Chemical Structure:



Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.73 g/mol

NAME AND QUANTITY OF EACH INGREDIENT:

UNIT DOSE

Ingredients	Qty./ tablet In mg	Use/Function
Active Ingredient		
Telmisartan USP	40.00	Anti-hypertensive
Hydrochlorothiazide USP	12.50	Anti-hypertensive
In Active Ingredients		
Micro Crystalline Cellulose BP	55.0	Disintegrant
Lactose BP	92.5	Binder
P.V.P.(K-30) BP	15.0	Binder
Magnesium Stearate BP	20.0	Lubricant
Talc BP	15.0	Diluent / Lubricant
Croscarmellose Sodium BP	10.0	Disintegrant
Hydroxy Propyl Methyl Cellulose (E-15) BP	--	Coating Agent
Propylene Glycol BP	--	Coating Agent
Color Titanium Dioxide BP	--	Coloring Agent
Isopropyl Alcohol BP	--	Vehicle
Methylene Chloride BP	--	Vehicle

Reference:
USP= United States Pharmacopeia
BP = British Pharmacopoeia
IHS= In- House Specification

3. PHARMACEUTICAL FORMS:
Oral film-coated tablets
White coloured, round shaped film-coated tablets

CLINICAL PARTICULARS:

4. INDICATIONS FOR USE:

Treatment of essential hypertension

Telmisartan - Hydrochlorothiazide fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

This medication is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. This product contains 2 medications: telmisartan and hydrochlorothiazide. Telmisartan belongs to a class of drugs called

angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so blood can flow more easily. Hydrochlorothiazide is a "water pill" (diuretic). It increases the amount of urine you make, especially when you first start the medication. It also helps to relax the blood vessels so that blood can flow more easily.

These medications are used together when 1 drug alone is not controlling your blood pressure. Your doctor may direct you to start taking the individual medications first, and then switch you over to this combination product if this is the best dose combination for you.

5. CONTRAINDICATIONS:

- Hypersensitivity to the active substances or to any of the excipients.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Second and third trimesters of pregnancy.
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

The concomitant use of VISOTEL with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

6. PRECAUTIONS :

Before taking this medication, tell your doctor or pharmacist if you are allergic to telmisartan or hydrochlorothiazide; or if you have any other allergies.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: kidney disease (such as renal artery stenosis), liver disease, bile duct blockage, loss of too much body water and/or minerals (dehydration), untreated mineral imbalance (such as low or high potassium), gout, lupus.

This drug may make you dizzy. Alcohol or marijuana can make you more dizzy. Do not drive, use machinery, or do anything that needs alertness until you can do it safely. Limit alcoholic beverages. Talk to your doctor if you are using marijuana.

Too much sweating, diarrhea, or vomiting may cause loss of too much body water (dehydration) and increase your risk of dizziness or light headedness. Report prolonged diarrhea or vomiting to your doctor. Be sure to drink enough fluids to prevent dehydration unless your doctor directs you otherwise.

Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

If you have diabetes, this medication may affect your blood sugar. Check your blood sugar regularly as directed and share the results with your doctor. Tell your doctor right away if you have symptoms of high blood sugar such as increased thirst/urination. Your doctor may need to adjust your diabetes medication, exercise program, or diet.

This product may affect your potassium levels. Before using potassium supplements or salt substitutes that contain potassium, consult your doctor or pharmacist.

7. SIDE EFFECTS:

Dizziness
Lightheadedness and
Tiredness
Flu symptoms
Nausea
Diarrhoea or
Cold symptoms such as stuffy nose, sneezing and sore throat

8. USES DURING PREGNANCY, LACTATION:

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 VISOTEL 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 drugs. 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.

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

There is limited experience with hydrochlorothiazides during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foeto and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

Because no information is available regarding the use of telmisartan during breast-feeding, VISOTEL 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 hydrochlorothiazide during breast feeding is not recommended. If hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

9. DRUG INTERACTIONS:
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases

have also been reported with angiotensin II receptor antagonists (including telmisartan/hydrochlorothiazide). Co-administration of lithium and VISOTEL is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives)
If these substances are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium.

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium).
If these medicinal products are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium and is, therefore, not recommended.

10. DOSAGES AND ADMINISTRATION:

Route of administration: Oral
VISOTEL should be used in patients whose blood pressure is not adequately controlled by telmisartan alone. Individual dose titration with each of the two components is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

- VISOTEL 40 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by telmisartan 40 mg.

VISOTEL is also available at the dose strengths 80 mg/ 12.5 mg and 80 mg/25 mg.

Special populations
Renal impairment
Periodic monitoring of renal function is advised
Hepatic impairment
In patients with mild to moderate hepatic impairment the posology should not exceed Telmisartan/Hydrochlorothiazide 40 mg/12.5 mg once daily. Telmisartan/Hydrochlorothiazide is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.
Elderly
No dose adjustment is necessary.
Paediatric population
The safety and efficacy of Telmisartan/Hydrochlorothiazide in children and adolescents aged below 18 have not been established. No data are available.
Method of administration
Telmisartan/Hydrochlorothiazide tablets are for once-daily oral administration and should be taken with liquid, with or without food.
Precautions to be taken before handling or administering the medicinal product

Telmisartan/Hydrochlorothiazide should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration

11. OVERDOSAGE:

There is limited information available for telmisartan with regard to overdose in humans. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, vomiting, increase in serum creatinine, and acute renal failure have also been reported. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment

Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

12. PHARMACOLOGY:

VISOTEL is a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. VISOTEL once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

MECHANISM OF ACTION

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics.

13. PHARMACOKINETICS:

Concomitant administration of hydrochlorothiazide and telmisartan does not appear to affect the pharmacokinetics of either substance in healthy subjects.

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 nonlinear 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/hydrochlorothiazide, 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.

Biotransformation

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans. After a single dose of ^{14}C-labelled telmisartan the glucuronide represents approximately 11 % of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan: Following either intravenous or oral administration of ^{14}C-labelled telmisartan most of the administered dose (>97 %) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1500 ml/min. Terminal elimination half-life was >20 hours.

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60 % of the oral dose is eliminated within 48 hours. Renal clearance is about 250-300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10-15 hours.

14. STORAGE:

Preserve in tight containers, at controlled room temperature and protect from moisture.
Do not use later than the date of expiry.
KEEP OUT OF REACH OF CHILDREN.

15. SHELF-LIFE:

36 MONTHS