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

Telmisartan 40mg, Hydrochlorothiazide 12.5mg & Amlodipine 5mg Tablets

OZOTEL®-AMH

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COMPOSITION:

Each uncoated bilayered tablet contains:

Telmisartan IP	40 mg
Hydrochlorothiazide IP	12.5 mg
Amlodipine Besilate IP eq. to Amlodipine	5 mg
Excipients	q.s.
Colour : Ponceau 4R	

PHARMACEUTICAL FORM

uncoated Tablet.

THERAPEUTIC INDICATION

For the treatment of essential hypertension.

DOSAGE AND ADMINISTRATION

Posology

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

It may be substituted for its individually titrated components for patients on telmisartan, amlodipine, and hydrochlorothiazide. 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: angiotensin receptor blockers, calcium channel blockers, and diuretics at their maximally tolerated, labeled, or usual dose.

Special populations

Geriatric Use

Telmisartan and Hydrochlorothiazide: 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 diseases or other drug therapy.

Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required.

Pediatric Use

Safety and effectiveness in paediatric patients has not been established.

Patients with Renal Impairment

Safety and effectiveness in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. Not recommended in patients with severe renal impairment. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment.

Patients with Hepatic Impairment

Telmisartan: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance and higher blood levels.

Hydrochlorothiazide: Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Amlodipine: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5mg. Since the dose of this film coated tablet is 40/5/12.5mg, It is not recommended in the hepatically impaired patients.

Method of administration: For oral use only.

The tablets should be swallowed whole with liquid and should not be chewed or crushed.

CONTRAINDICATIONS

Contraindicated in patients with known hypersensitivity to any of the active ingredients or excipients.

- In patients with anuria.
- Do not co-administer with aliskiren in patients with diabetes.

Amlodipine is contraindicated in patients with: 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), severe hypotension, haemodynamically unstable heart failure after acute myocardial. infarction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warning : Fetal Toxicity

When pregnancy is detected, discontinue this tablet as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

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 the use of this tablet as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice, thrombocytopenia.

Hypotension

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initialization of treatment with this tablet. Correct volume or salt depletion prior to administration of this film tablet.

Amlodipine: Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on this tablet. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on this tablet.

Patients with Hepatic Failure

It is not recommended in hepatically impaired patients.

Dual Blockade of the Renin-Angiotensin-Aldosterone System and Changes in Renal Function

Dual blockade of the renin-angiotensin-aldosterone system (RAS) with angiotensin blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and renal impairment.

In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on this tablet and other agents that affect the RAS.

Do not co-administer aliskiren with this tablet in patients with diabetes. Avoid concomitant use of aliskiren with this tablet in patients with renal impairment (GFR <60mL/min/1.73 m2).

Electrolytes and Metabolic Disorders

Drugs, including telmisartan, that inhibit the renin-angiotensin system can cause hyperkalemia, particularly in patients with renal insufficiency, diabetes, or combination use with other angiotensin receptor blockers or ACE inhibitors and the concomitant use of other drugs that raise serum potassium levels.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because telmisartan decreases uric acid, telmisartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Hypersensitivity Reaction

Hydrochlorothiazide: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Postsympathectomy Patients

The antihypertensive effects of hydrochlorothiazide may be enhanced in the postsympathectomy patient.

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Heart Failure

Closely monitor patients with heart failure.

DRUG INTERACTION

Telmisartan and Hydrochlorothiazide

Agents Increasing Serum Potassium: Co-administration of telmisartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of thiazide diuretics or angiotensin II receptor antagonists, including telmisartan. Monitor lithium levels in patients receiving this tablet and lithium.

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Monitor digoxin levels in patients taking concomitant this tablet and digoxin.

Aliskiren: Do not co-administer aliskiren with this tablet in patients with diabetes. Avoid use of aliskiren with this tablet in patients with renal impairment.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):

Telmisartan

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs may be attenuated by NSAIDs. Therefore, monitor renal function periodically in patients receiving this tablet and NSAIDs.

Hydrochlorothiazide

Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Therefore, when this tablet and nonsteroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

Antidiabetic drugs (oral agents and insulin)

Dosage adjustment of the antidiabetic drug may be required when co-administered with hydrochlorothiazide.

Cholestyramine and Colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

Amlodipine

CYP3A4 Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is coadministered with CYP3A4 inducers.

Sildenafil: Monitor for hypotension when sildenafil is co-administered with amlodipine.

Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppr essants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when coadministered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

PREGNANCY AND LACTATION

Pregnancy

This tablet can cause fetal harm when administered to a pregnant woman. 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.

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

In patients taking this tablet during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue this tablet, unless it is considered lifesaving for the mother. 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 this tablet for hypotension, oliguria, andhyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Lactation

There is no information regarding the presence of this tablet or telmisartan in human milk, the effects on the breastfed infant or the effects on milk production.

Telmisartan is present in the milk of lactating rats. Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with this tablet.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Use of this tablet may have minor or moderate influence on the ability to drive and use machines. If patients taking this tablet suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

UNDESIRABLE EFFECTST

Telmisartan and Hydrochlorothiazide

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (≥1/10,000 to <1/1,000). The overall incidence of adverse reactions reported with Telmisartan/Hydrochlorothiazide was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients randomised to receive telmisartan plus hydrochlorothiazide (835) or telmisartan alone (636). Dose-relationship of adverse reactions was not established and they showed no correlation with gender, age or race of the patients.

Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance.

The following adverse reactions are discussed elsewhere in labeling:

- Hypotension
- Renal Impairment
- Electrolytes and Metabolic Disorders

Common adverse effects ≥2%: Fatigue, influenza like symptoms, dizziness, nausea, diarrhea, sinusitis and upper respiratory tract infection.

Amlodipine

Gingival Hypertrophy and Alopecia as an adverse drug reaction has been reported with amlodipine.

The most commonly reported adverse reactions during amlodipine treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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 the order of decreasing seriousness:

Blood and lymphatic system disorders: Very rare: Leukocytopenia, thrombocytopenia.

Immune system disorders: Very rare: Allergic reactions.

Metabolism and nutrition disorders: Very rare: hyperglycaemia.

Psychiatric disorders: Uncommon: Depression, mood changes (including anxiety), insomnia. Rare: confusion.

Nervous system disorders: common: Somnolence, dizziness, headache (especially at the beginning of the treatment). Uncommon: Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia. Very rare: Hypertonia, peripheral neuropathy.

Ear and labyrinth disorders: Common: Visual disturbance (including diplopia). Uncommon: Tinnitus.

Cardiac and Vascular disorders: Common: Palpitations. Uncommon; arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation). very rare: Myocardial infarction.

Vascular disorders: Common: flushing. Uncommon: hypotension. Very rare: vasculitis.

Respiratory, thoracic and mediastinal disorders: Common: dyspnoea. Uncommon: cough, rhinitis.

Gastrointestinal disorders: Common: Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation). Uncommon: Vomiting, dry mouth. Very rare: Pancreatitis, gastritis, gingival hyperplasia.

Hepatobiliary disorders: Very rare: Hepatitis, jaundice, hepatic enzyme increased.

Skin and subcutaneous tissue disorders: Uncommon: Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria. Very rare: Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity. Unknown: Toxic Epidermal Necrolysis.

Musculoskeletal and connective tissue disorders: Common:Ankle swelling, muscle cramps. Uncommon: Arthralgia, myalgia, back pain.

Renal and urinary disorders: Uncommon: Micturition disorder, nocturia, increased urinary frequency.

Reproductive system and breast disorders: Uncommon: Impotence, gynaecomastia.

General disorders and administration site conditions: Very common: Oedema. Common: Fatigue, asthenia. Uncommon: Chest pain, pain, malaise.

Investigations: Uncommon: Weight increased, weight decreased.

Exceptional cases of extrapyramidal syndrome have been reported.

OVERDOSE

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.

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. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Angiotensin II receptor blocker, Thiazide diuretics, and Calcium channel blockers - Dihydropyridine derivatives.

This tablets have been shown to be effective in lowering blood pressure. It is a combination of three drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, telmisartan; and an thiazide diuretic, hydrochlorthiazide (HCZ). The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. This combination, once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan

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 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. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.

Hydrochlorothiazide

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. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

● The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

● The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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.

Hydrochlorothiazide, Following oral administration of telmisartan and 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 %.

Amlodipine, After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The bioavailability of amlodipine is not affected by food intake.

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.

Amlodipine, The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Metabolism

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 14C-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.

Amlodipine, is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound.

Excretion

Telmisartan, Following either intravenous or oral administration of 14C-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.

Amlodipine, About 60% of amlodipine metabolites excreted in the urine. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

INCOMPATIBILITY

None stated.

STORAGE INSTRUCTIONS

Store protected from light, at a temperature not exceeding 30°C.

Keep the medicines out of reach of children.

Important : Moisture sensitive tablets - Do not remove from strip until immediately before administration.

Marketed by:
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