SUMMARY OF PRODUCT CHARACTERISTICS OF TELMICOS-AMH TABLET

1. Name of the medicinal product

Telmicos-AMH 40/12.5/5 mg tablets

2. Qualitative and quantitative composition

Each tablet contains 40 mg Telmisartan 12.5 mg Hydrochlorothiazide and 5 mg of Amlodipine Besylate

3. Pharmaceutical form

Uncoated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Telmicos AMH tablet is used for hypertension, coronary artery disease, chronic stable angina, vasospastic angina, fluid retention, heart failure, liver failure, kidney failure.

4.2 Posology and method of administration

Should be taken once daily preferably in the morning.

Telmicos AMH may be substituted for its individually titrated components for patients on Telmisartan, Amlodipine, and Hydrochlorothiazide. Telmicos AMH 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.

4.3 Contraindications

Telmicos AMH is contraindicated in patients with known hypersensitivity to any component of this product.

Precautions and warnings

Before using Telmicos AM H Tablet, inform your doctor about any medications you are taking, like any allergies, pre-existing diseases, and current health conditions (e.g. pregnancy, upcoming surgery, etc.). Take as directed by your doctor as the dosage is based on your condition. Tell your doctor if your condition persists or worsens. Important counseling points are listed below.

- Avoid taking hydrochlorothiazide at bedtime because it makes you urinate more often
- Consult your doctor if you experience dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, muscle pains or cramps
- Do not chew, divide or crush the tablets
- Drink adequate amount of liquid to avoid becoming dehydrated or overheated

- Get your blood pressure, potassium and kidney function checked 1 week after starting this medicine
- Hepatic impairment
- Inform your doctor of any other medications you may be taking
- Seek medical attention immediately if you experience increased chest pain or any of the side effects listed below for a longer duration.
- Severe aortic stenosis
- Severe obstructive coronary artery disease

4.4 Interaction with other medicinal products and other forms of interaction

Tell your doctor about all the drugs, vitamins, and herbal supplements you are using, so that you doctor can help you prevent or manage drug interactions. Telmicos AMH Tablet may interact with the following drugs and products:

- Acetylsalicylic acid, Alcohol, Amifostine, Amiloride, CYP3A4 inhibitors, Cholestyramine, Colestipol, Corticosteroids, Cyclosporine etc

4.5 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 Telmicos-AMH 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 hydrochlorothiazide 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 foetal 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 TELMICOS-AMH during breast-feeding, TELMICOS-AMH 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 TELMICOS-AMH during breast feeding is not recommended. If TELMICOS-AMH 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.

4.6 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 such as Telmicos-AMH.

4.7 Undesirable effects

The following are possible side-effects that may occur when taking Telmicos AMH Tablet. Consult your doctor if you observe any of the following side-effects, especially if they persist for a long time.

- Cough
- Swelling of legs and feet
- Drowsiness
- Nausea
- Abdominal pain
- Dizziness
- Flushing
- Arrhythmia
- Rapid heartbeat
- Hypotension, Visual disturbances

WARNING
TELMICOS-AMH Tablets should not be taken during pregnancy

4.8 Overdose

Telmisartan Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

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.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacology of 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.There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (> 3,000 fold) for the AT_1 receptor than for the AT_2 receptor.Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.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.

Pharmacology of Hydrochlorothiazide

- It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule.
- The major site of action in the nephron appears on an electroneutral Na^+-Cl^- co-transporter by competing for the chloride site on the transporter.
- By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss.
- Thiazides increase the reabsorption of calcium in this segment.
- Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.

Pharmacology of Amlodipine Besylate

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.

1) 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.

2) 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).

5.2 Pharmacokinetic properties

Pharmacokinetics of Telmisartan

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. 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 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) 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% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (> 99.5%), mainly albumin and α1 - 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.

Metabolism and Elimination

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (> 97%) was eliminated unchanged in 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 acyl glucuronide; 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 > 800 mL/min. Terminal half-life and total clearance appears to be independent of dose.

Pharmacokinetics of Hydrochlorothiazide

Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/mL following oral doses of 12.5 to 100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged.

Pharmacokinetic of Amlodipine Besylate

Absorption, distribution, plasma protein binding***:*** 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 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. The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

6. Pharmaceutical particulars

6.1 List of excipients

Ludipress IH
FLOCEL 101 USP
Calcium hydrogen phosphate BP
Sodium starch glycollate BP
Magnesium stearate BP
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a dry place below 30ºC. Protect from light

6.5 Nature and contents of container

ALU/ALU Blister Packing

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Registrant

Cosmos Limited

8. Marketing authorisation holder

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