SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product:

TELMI TAB – 40 AMH

(TELMISARTAN 40 MG, AMLODIPINE 5 MG AND HYDROCHLOROTHIAZIDE 12.5 MG TABLETS)

2. Qualitative and Quantitative composition:

Composition:

Each film coated tablet contains :

Telmisartan USP 40 mg

Amlodipine Besylate USP Equivalent to Amlodipine 5 mg

Hydrochlorothiazide USP 12.5 mg

Sunset Yellow

Excipients Q. S.

3. Pharmaceutical Form:

Tablet for Oral Administration.

Orange coloured, circular shaped, biconvex, film coated tablets having breakline on one side and plain on other side.

4. Clinical Particulars:

4.1 Therapeutic Indications:

Treatment of essential hypertension in adults:

For the treatment of essential hypertension.

This fixed dose combination is not indicated for initial therapy.

4.2 Posology and method of administration:

Dose once daily. Telmi Tab AMH may be substituted for its individually titrated components for patients on telmisartan, amlodipine, and hydrochlorothiazide. Telmi Tab 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.

Special Populations:

Pediatric Use Safety and effectiveness in paediatric patients has not been established 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. 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 (t 1/2) 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 Telmi Tab AMH is 40/5/12.5mg, Telmi Tab AMH is not recommended in hepatically impaired patients.

4.3 Contraindications:

Telmi Tab AMH is contraindicated in patients with known hypersensitivity to any component of this product (see Warnings and Precautions), in patients with anuria. Do not co-administer with aliskiren in patients with diabetes

4.4 Special warning and precaution for use:

Fetal Toxicity

WARNING: FETAL TOXICITY When pregnancy is detected, discontinue Telmi Tab AMH 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 Telmi Tab AMH 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 Telmi Tab AMH. Correct volume or salt depletion prior to administration of Telmi Tab AMH. 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 Telmi Tab AMH. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Telmi Tab AMH.

Patients with Hepatic Failure Telmi Tab AMH 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 Telmi Tab AMH and other agents that affect the RAS. Do not co-administer aliskiren with Telmi Tab AMH in patients with diabetes. Avoid concomitant use of aliskiren with Telmi Tab AMH in patients with renal impairment (GFR <60 mL/min/1.73 m^2)

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.

4.5 Interaction with other medicinal products and other forms of 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 Telmi Tab AMH 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 Telmi Tab AMH and digoxin. Aliskiren Do not co-administer aliskiren with Telmi Tab AMH in patients with diabetes. Avoid use of aliskiren with Telmi Tab AMH in patients with renal impairment.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): Telmisartan Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX2 Inhibitors): 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 Telmi Tab AMH 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 Telmi Tab AMH 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. Immunosuppressants 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.

4.6 Pregnancy and Lactation :

Pregnancy:

Telmi Tab AMH 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 Telmi Tab AMH 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 Telmi Tab AMH, 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 Telmi Tab AMH 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 Telmi Tab AMH 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 Telmi Tab AMH

4.7 Effects on the ability to drive and use machines:

This medicinal product has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines

4.8 Undesirable effects:

Telmisartan and hydrochlorothiazide 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. The most common adverse reaction to amlodipine is oedema which occurred in dose related manner. Other adverse experiences not dose related but reported with an incidence >1.0% are fatigue, nausea, abdominal pain and somnolence.

4.9 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.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers.

Telmisartan: ATC code: C09DCA07

Amlodipine: ATC code: C07FB07

Hydrochlorothiazide: ATC Code: C03AA03

Telmitab AMH combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Telmitab AM once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions. In humans, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours. After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo

controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent. In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of substances representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril). Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension. The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments. Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy. ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. 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. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout. Use in patients with heart failure Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology. A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure. In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Telmisartan/Amlodipine In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and ≤119 mmHg), treatment with each combination dose of Telmitab AM resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components. Telmitab AMH showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of –21.8/–16.5 mmHg (40 mg/5 mg), –22.1/–18.2 mmHg (80 mg/5 mg), –24.7/–20.2 mmHg (40 mg/10 mg) and –26.4/–20.1 mmHg (80 mg/10

mg). The reduction in diastolic blood pressure. generalised oedema, and oedema) were consistently lower in patients who received Telmitab AMH as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with Telmitab AMH 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Telmitab AMH 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Telmitab AMH was similar irrespective of age and gender, and was similar in patients with and without diabetes. Telmitab AMH has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease. Paediatric population The European Medicines Agency has waived the obligation to submit the results of studies with Telmitab AMH in all subsets of the paediatric population in hypertension.

Hydrochlorothiazide

It 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 rennin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the reninangiotensin-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.

Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination:

The rate and extent of absorption of Telmitab AMH are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Absorption :

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to

approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. 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 %. Amlodipine bioavailability is not affected by food ingestion.
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 largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 l. The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.
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 the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.
Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.
Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half life of >20 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.
After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound.
Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration f. or 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine Linearity/non-linearity. The small reduction in AUC for telmisartan is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels.

Cmax and to a lesser extent AUC increase disproportionately at doses above 40 mg. Amlodipine exhibits linear pharmacokinetics.
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.

Paediatric population (age below 18 years) No pharmacokinetic data are available in the paediatric population. Gender Differences in plasma concentrations of telmisartan were observed, with Cmax and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males. Elderly The pharmacokinetics of telmisartan do not differ in young and elderly patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.
Renal impairment: In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Hepatic impairment Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40-60 % in AUC.

5.3 Pre-clinical Safety:

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested. Preclinical data available for the components of this fixed dose combination are reported below.
Telmisartan: In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and

angiotensin II receptor antagonists, were prevented by oral saline supplementation. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance. No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offspring such as lower body weight and delayed eye opening was observed. There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

Amlodipine: Reproductive toxicology Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg. Impairment of fertility There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 10 mg/day on an mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Carcinogenesis, mutagenesis Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. *Based on patient weight of 50 kg.

6.Pharmaceutical Particulars:

6.1 List of Excipients: Mannitol, Microcrystalline Cellulose, Iso Propyl Alcohol, MCC pH-102, Croscarmellose Sodium, Aerosil, Talcum, Sodium Stearyl fumarate, HPMC CE-15, Sunset Yellow FCF, Propylene Glycol, Isopropyl alcohol, Methylene chloride, Castor oil.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf Life:

36 months.

6.4 Special Precautions for storage:

Keep all medicines away from the reach of children. Store in cool, dark & dry place at a temperature below 30°C. Protected from moisture.

6.5 Nature and contents of container :

ALU- ALU Blister pack of 3 x 10 Tablets

ALU- ALU Blister pack of 1 x 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

GALAXY PHARMACEUTICALS

Building no. 37, Gala No, 1, Bhiwandi, Thane (Mumbai)

Maharashtra- 421302

INDIA

8. Marketing Authorization Number: ----

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

10. Date of revision of text: 15.04.2023