MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.1 Name of the medicinal product:

TELSARTAM 80/10

1.2 (Invented) name of the medicinal product:

Generic Name/INN Name:

Telmisartan and Amlodipine Tablets USP

1. 2 Strength:

Each bilayer uncoated tablet contains:

Telmisartan USP 80 mg

Amlodipine Besylate USP

Eq. to Amlodipine 10 mg

Excipients q.s.

Colour: Indigocarmine

1.3 Pharmaceutical form:

Oral solid dosage form- Bilayer Uncoated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specifi-cation	Label Claim (mg)	Std Qty./ Tablet (mg)	%w/w	Function
Layer 1						
Sifting						
1	Lactose Monohydrate	BP	--	289.200	52.58	Diluent
Granulation (Top Spray)						
2	Telmisartan	USP	80.00	80.000	14.55	API
3	Povidone K-30	BP	--	6.000	1.09	Binder
4	Sodium Hydroxide	BP	--	6.800	1.24	pH adjusting agent
5	Meglumine	USP	--	18.000	3.27	pH adjusting

						agent
6	Purified Water	BP	--	q.s.	NA	Binding solvent
Lubrication						
7	Sodium stearyl fumarate	BP	--	10.000	1.82	Lubricant
Weight of Telmisartan layer				**410.00**	**74.54**	
Layer 2						
Dry Mixing for Amlodipine Besylate						
8	Amlodipine Besylate Eq. to Amlodipine	USP	10.000	13.900	2.53	API
9	Microcrystalline Cellulose PH 102	BP	--	98.800	17.96	Diluent
10	Pregelatinised Starch	BP	--	25.000	4.55	Diluent
11	Indigocarmine	IH	--	1.000	0.18	colorant
12	Colloidal Anhydrous Silica	BP	--	0.300	0.05	Glidant
Lubrication						
13	Magnesium Stearate	BP	--	1.000	0.18	Lubricant
Weight of Amlodipine layer				**140.00**	**25.45**	
Total weight of bilayer tablet				**550.00**	**100.0**	

3 Pharmaceutical form:

Dosage Form: Oral solid dosage form- Bilayer Uncoated Tablet

Visual & Physical characteristics of the product:

White to off-white and blue colored, bilayer, capsule shape, biconvex, uncoated tablets, plain on both sides. White colour layer may contain blue colour specks.

4. Clinical particulars

4.1. Therapeutic indications:

Treatment of essential hypertension.

4.2. Posology and method of administration:

Telmisartan is an effective treatment of hypertension in once daily doses of 20-80 mg while amlodipine is effective in doses of 2.5-10 mg. Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of telmisartan

and amlodipine tablets is 80/10 mg once daily. The adverse reactions of telmisartan are uncommon and independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. Telmisartan and Amlodipine tablets may be taken with or without food.

Replacement Therapy

Patients receiving amlodipine and telmisartan from separate tablets may instead receive Telmisartan and Amlodipine tablets containing the same component doses once daily. When substituting for individual components, increase the dose of Telmisartan and Amlodipine Tablets if blood pressure control has not been satisfactory.

Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy

Telmisartan and amlodipine tablets may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another angiotensin receptor blocker) alone.

Patients treated with 10 mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to Telmisartan and Amlodipine tablets once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Initial Therapy

A patient may be initiated on Telmisartan and amlodipine tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of Telmisartan and Amlodipine tablets is 40/5 mg once daily.

Initial therapy with Telmisartan and Amlodipine tablets is not recommended in patients ≥75 years old or with hepatic impairment.

Correct imbalances of intravascular volume- or salt-depletion, before initiating therapy with Telmisartan and Amlodipine Tablets.

Dosing in Specific Populations

Renal Impairment

No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

Hepatic Impairment

In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients with hepatic impairment.

Patients 75 Years of Age and Older

In most patients, initiate amlodipine therapy at 2.5 mg. Titrate slowly in patients 75 years of age and older.

4.3. Contraindications:

Known hypersensitivity (e.g., anaphylaxis or angioedema) to Telmisartan, Amlodipine.

4.4. Special warnings and precautions for use:

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan and Amlodipine Tablets as soon as possible.

Hypotension

Telmisartan

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 initiation of therapy with Telmisartan and Amlodipine Tablets USP. Either correct this condition prior to administration of Telmisartan and Amlodipine Tablets USP, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A

transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine

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

Hyperkalemia

Telmisartan

Hyperkalemia may occur in patients on ARBs (angiotensin renin blockers), particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Patients with Impaired Hepatic Function

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. Initiate telmisartan at low doses and titrate slowly in these patients.

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 2.5 mg in patients with hepatic impairment. The lowest dose of Telmisartan and Amlodipine Tablets USP is 40/5 mg; therefore, initial therapy with Telmisartan and Amlodipine Tablets USP is not recommended in hepatically impaired patients.

Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function

may depend on the activity of the renin-angiotensin aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

Dual blockade of the renin angiotensin aldosterone system with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two renin angiotensin aldosterone system inhibitors concomitantly. In general, avoid combined use of renin angiotensin aldosterone system inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and Amlodipine Tablets USP and other agents that affect the renin angiotensin aldosterone system. Do not co-administer aliskiren with Telmisartan and Amlodipine Tablets USP in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan and Amlodipine Tablets USP in patients with renal impairment.

Risk of Myocardial Infarction or Increased Angina

Amlodipine

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

Heart Failure

Amlodipine Closely monitor patients with heart failure.

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4.5. Interaction with other medicinal products and other forms of interaction:

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered. No drug interaction studies have been conducted with Telmisartan and Amlodipine Tablets USP and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of Telmisartan and Amlodipine Tablets USP

Drug Interactions with Telmisartan

Aliskiren:

Do not co-administer aliskiren with Telmisartan and Amlodipine Tablets USP in patients with diabetes. Avoid use of aliskiren with Telmisartan and Amlodipine Tablets USP in patients with renal impairment.

Digoxin:

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range. Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use. Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 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 angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Drug Interactions with Amlodipine

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immuno suppressants:

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when coadministered. Frequent monitoring of trough blood levels of cyclosporin and tacrolimus and dose adjustment when appropriate is recommended. The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil. Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, and warfarin.

CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors. CYP3A4 Inducers No information is available on the quantitative effects of CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort) on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

4.6. Pregnancy and Lactation:

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Telmisartan and Amlodipine Tablets USP can cause foetal harm when administered to pregnant woman. Use of drugs that act on the reninangiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications. Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

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 the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. In patients taking Telmisartan and Amlodipine Tablets USP during pregnancy, perform serial ultrasound examinations to assess the intraamniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Telmisartan and Amlodipine Tablets USP 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 Telmisartan and Amlodipine Tablets USP for hypotension, oliguria, and hyperkalemia. 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/or substituting for disordered renal function.

LACTATION

There is no information regarding the presence of Telmisartan and Amlodipine Tablets USP or telmisartan in human milk, the effects on the breastfed infant, or

the effects on milk production. Limited published studies report that amlodipine is present in human milk. However, there is insufficient information to determine the effects of amlodipine on the breastfed infant. There is no available information on the effects of amlodipine on milk production. 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 Telmisartan and Amlodipine Tablets USP

PEDIATRIC USE

Safety and effectiveness of Telmisartan and Amlodipine Tablets USP in pediatric patients have not been established. Neonates with a history of in utero exposure to Telmisartan and Amlodipine Tablets USP: 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/or substituting for disordered renal function.

GERIATRIC USE

Telmisartan

No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine

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 disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%, and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan.

The dose of Telmisartan and Amlodipine Tablets USP is 40/5 mg; therefore, initial therapy with Telmisartan and Amlodipine Tablets USP is not recommended in patients 75 years of age and older.

Hepatic Insufficiency

Monitor carefully and up titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The dose of Telmisartan and Amlodipine Tablets USP is 40/5 mg; therefore, initial therapy with Telmisartan and Amlodipine Tablets USP is not recommended in hepatically impaired patients.

4.7. Effects on ability to drive and use machines:

Telmisartan and Amlodipine Tablets USP 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

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g., toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal

outcome). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine

Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

4.9. Overdose:

Telmisartan

Limited data are available with regard to over dosage in humans. The most likely manifestations of over dosage 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.

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, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. 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 properties:

5.1. Pharmacodynamic properties:

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers,

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ATC code: C09DB04.

Telmisartan and Amlodipine Tablets USP 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.

Telmisartan and Amlodipine Tablets USP 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.

Amlodipine Besylate:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following: Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise. Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

5.2. Pharmacokinetic properties:

General:

Telmisartan:

Following oral administration, peak concentrations (Cmax) of Telmisartan are reached in 0.5-1 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 20-160 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 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Amlodipine Besylate:

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure. Pediatric Patients: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Metabolism and Elimination:

Telmisartan:

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 acylglucuronide; 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

Total plasma clearance of Telmisartan is > 800 mL/min. Terminal half-life and total clearance appears to be independent of dose.

Amlodipine Besylate:

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

Distribution:

Telmisartan:

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.

Amlodipine Besylate:

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.

5.3 Preclinical safety data

In preclinical safety studies performed with co-administration of telmisartan and Amlodipine in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

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

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

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with Amlodipine have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with

Amlodipine has failed to show an association between its use and an increase in neoplasms.

6. Pharmaceutical particulars:

6.1. List of Excipients:

Meglumine

Sodium Hydroxide

Povidone K-30

Pregelatinised Starch

Colloidal Anhydrous Silica

Magnesium Stearate

Microcrystalline cellulose pH 102

Indigocarmine

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store below 30 °C. Protect from moisture.

6.5. Nature and contents of container:

Primary Pack: 7 Tablets are packed in one Alu-Alu blister pack.

Secondary Pack: Such 4 blisters are packed in one mono carton along with package insert.

6.6. Special precautions for disposal:

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

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7. Applicant

Evans Therapeutics Limited.

No. 24, Abimbola Way, Isolo Industrial Estate, Isolo. Lagos, Nigeria

E-mail: olanihun.temitope@evanstherapeutics.com

Name and Address of manufacturer:

Name : Bharat Parenterals Limited

Address : Survey No.144 & 146, Jarod Samlaya Road, Village Haripura Tal-Savali Dist .Vadodara 391520Gujarat State India

E-mail : bplbrd@yahoo.com, info@bplindia.in, bplbrd@bplindia.in