1.3.1 Summary of Pharmaceutical characteristics

1.0 Name of Medicinal Product

TELAM 80/5 (Telmisartan & Amlodipine Tablets USP 80/5 mg)

2.0 Qualitative-Quantitative Formula

QUALITATIVE AND QUANTITATIVE COMPOSITION	
Product Name	**TELAM 80/5**
Generic Name	Telmisartan & Amlodipine Tablets USP 80/5 mg
Label claim	Each Uncoated Bilayered tablet Contains: Telmisartan USP 80mg Amlodipine Besylate USP Eq. to Amlodipine 5mg Excipients q.s **Colour:** Ponceau 4R

S. No.	Ingredients	Claim mg	O.A. (%)	Spec.	Qty/Tab mg	Qty/Tab (%)	Qty./100000 Tabs. (Kg)
Layer 1 -							
MIXING / GRANULATION:							
01	Mannitol**	------	------	BP	78.000	17.33	7.800
02	Telmisartan*	80mg	------	USP	80.000	17.78	8.000
03	Meglumine	------		BP	76.000	16.89	7.600
SOLUTION PREPARATION OF POTASSIUM HYDROXIDE:							
04	Potassium Hydroxide	------	------	BP	20.000	4.44	2.000
05	Purified Water#	------	------	BP	----	---	2.000 Ltr
BINDING:							
06	Methylene Chloride#	------	------	BP	---	---	6.000
LUBRICATION / BLENDING:							
07	Kyron T-314	------	------	IH	10.000	2.22	1.000
08	Purified Talc	------	------	BP	6.000	1.33	0.600
09	Sodium Starch Glycolate	------	------	EP/BP	8.000	1.78	0.800
10	Colloidal Anhydrous Silica	------	------	BP	8.000	1.78	0.800
11	Magnesium Stearate	------	------	BP	4.000	0.89	0.400
			Total Weight		**290.00mg**	**64.44%**	**29.000 kg.**
* Quantity based on 100% basis. Calculate actual qty based on actual potency. ** Compensate the excess qty of API with Mannitol. # does not remain in final product.							
Layer 2 -							
MIXING / GRANULATION:							
12	Dibasic Calcium Phosphate**	------	------	USP	63.185	14.04	6.3185
13	Maize Starch***	------	------	BP	70.000 Eq. to 63.000	14.00	7.000 Eq. to 6.300
BINDING:							

14	Methyl Hydroxybenzoate	------	------	BP	0.400	0.09	0.040
15	Propyl Hydroxybenzoate	------	------	BP	0.100	0.022	0.010
16	Maize Starch***	------	------	BP	10.600 Eq. to 9.540	2.12	1.060 eq. to 0.954
17	Col. Ponceau 4R BIS (SUPRA)	------	------	IH	0.200	0.044	0.020
18	Purified Water#	------	------	BP	----	----	2.500 Ltr
LUBRICATION / BLENDING:							
19	Amlodipine Besylate* Eq. to Amlodipine	5 mg	------	USP	6.935	1.54	0.6935
20	Croscarmellose Sodium (Primellose)	------	------	EP	4.000	0.89	0.400
21	Purified Talc	------	------	BP	5.320	1.18	0.532
22	Colloidal Anhydrous Silica	------	------	BP	2.000	0.44	0.200
23	Magnesium Stearate	------	------	BP	5.320	1.18	0.532
Total Weight					**168.06 eq. to**	**35.56%**	**16.806 eq. to 16.000 Kg.**
Total Weight of Layer 1st + Layer 2nd					**450 mg (290 mg +160 mg)**	**100.00%**	**45.000 Kg.**

* Quantity based on 100% basis. Calculate actual qty based on actual potency.
** Compensate the excess qty of API with Di basic calcium phosphate (Di-hydrate).
***10% extra qty of Starch taken to compensate the losses in drying process.
#does not remain in final product.
Abbreviations: O.A.-Over Ages, **Qty.:** Quantity, **Tab.:** Tablet, **Spec.:** Specification. **IH**: In-House, **BP**: British Pharmacopoeia, **USP**: United States Pharmacopoeia.

3. Pharmaceutical Form: Solid Oral (Uncoated Bilayered Tablets)

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy

Telmisartan & Amlodipine 80 mg/5 mg is indicated in adults whose blood pressure is not adequately controlled on amlodipine 5 mg alone.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Telmisartan & Amlodipine containing the same component doses.

4.2 Posology and method of administration

Posology

The recommended dose of this medicinal product is one tablet per day.

The maximum recommended dose is one tablet 80 mg telmisartan/10 mg amlodipine per day. This medicinal product is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Add on therapy

TELAM 80/5 may be administered in patients whose blood pressure is not adequately controlled with Telmisartan & Amlodipine Tablets 40/5.

Individual dose titration with the components (i.e. amlodipine and Telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to TELAM 80/5 once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy

Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of TELAM 80/5 containing the same component doses in one tablet once daily.

Elderly (> 65 years)

No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using Telmisartan/amlodipine in such patients as amlodipine and telmisartan are not dialyzable.

No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

TELAM 80/5 is contraindicated in patients with severe hepatic impairment.

[redacted]

TE[redacted]

4.3 C[redacted]

- Hy[redacted] listed[redacted]
- Second [redacted]
- Biliary obs[redacted]
- Shock (includ[redacted]
- Obstruction of the[redacted]
- Haemodynamically u[redacted]
- The concomitant use of[redacted] patients with diabetes mellit[redacted]

4.4 Special warning and precauti[redacted]

Pregnancy

Angiotensin II receptor antagonists s[redacted] receptor antagonist therapy is cons[redacted] alternative antihypertensive treatmer[redacted] pregnancy is diagnosed, treatment w[redacted] and, if appropriate, alternative therap[redacted]

Hepatic impairment

[redacted]

insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. telmisartan/amlodipine should therefore be used with caution in these patients.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system (RAAS).

Renal impairment and kidney transplantation

When telmisartan/amlodipine is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of telmisartan. If hypotension occurs with telmisartan/amlodipine, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the

renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction

There are no data to support the use of telmisartan/amlodipine in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. Hyperkalaemia may be fatal in the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels,

and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the

renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated. The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the

renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extensive trauma).

Serum potassium should be monitored closely in these patients.

Other

As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interactions

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination

No drug interaction studies have been performed.

To be taken into account with concomitant use

Other antihypertensive medicinal products

The blood pressure lowering effect of telmisartan/amlodipine can be increased by concomitant use of other

antihypertensive medicinal products.

Medicinal products with blood pressure lowering potential

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other antihypertensive agents acting on the renin-angiotensin-aldosterone system (RAAS)

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non- selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Ramipril

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Concomitant use to be taken into account

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49 %) and in trough concentration (20 %) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors

With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Grapefruit and grapefruit juice

Concomitant administration of 240 ml of rapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

Concomitant use to be taken into account

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

Others

Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal

products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Telmisartan

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.

Studies with telmisartan 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 medicinal products. 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.

Amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Because no information is available regarding the use of telmisartan during breast-feeding, telmisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility

No data from controlled clinical studies with the fixed dose combination or with the individual components are available.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.

In preclinical studies, no effects of telmisartan on male and female fertility were observed. Similarly, no effects on male and female fertility were reported for amlodipine.

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and *in vitro* studies. No clinical relevance has been established.

4.7 Effects on ability to drive and use machine

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

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with TELAM 80/5 as well, even if not observed in clinical trials or during the post-marketing period.

Tabulated list of adverse reactions

The safety and tolerability of TELAM 80/5 has been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of who received telmisartan in combination with amlodipine.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare

System Organ Class	TELAM 80/5	Telmisartan	Amlodipine
Infections and infestations			
Uncommon		upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis	
Rare	cystitis	sepsis including fatal outcome 1	
Blood and lymphatic system disorders:			
Uncommon		anaemia	
Rare		thrombocytopenia, eosinophilia	
Very rare			leukocytopenia, thrombocytopenia
Immune system disorders:			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
Metabolism and nutrition disorders			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in diabetic patients)	
Very rare			hyperglycaemia

Psychiatric disorders			
Uncommon			
Rare	depression, anxiety, insomnia		confusion
Nervous system disorders			
Common	dizziness		
Uncommon	somnolence, migraine, headache, paraesthesia		
Rare	syncope, peripheral neuropathy,hypoaesthesia, dysgeusia, tremor		
Very rare			extrapyramidal syndrome
Eye disorders			
Uncommon			visual impairment
Rare		visual disturbance	
Ear and labyrinth disorders			
Uncommon	vertigo		tinnitus
Cardiac disorders			
Uncommon	bradycardia, palpitations		
Rare		tachycardia	
Very rare			myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders			
Uncommon	hypotension, orthostatic hypotension, flushing		
Very rare			vasculitis
Respiratory, thoracic and mediastinal disorders			
Uncommon	cough	dyspnoea	dyspnoea, rhinitis
Very rare	interstitial lung disease3		
Gastrointestinal disorder			

Uncommon	abdominal pain, diarrhoea, nausea	flatulence	
Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth	stomach discomfort	
Very rare			pancreatitis, gastritis
Hepato-biliary disorders			
Rare		hepatic function abnormal, liver disorder 2	
Very rare			hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders			
Uncommon	pruritus	hyperhidrosis	alopecia, purpura, skin discolouration, hyperhidrosis
Rare	eczema, erythema, rash	angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria	
Very rare			angioedema, Erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			
Uncommon	arthralgia, muscle spasms (cramps in legs), myalgia		
Rare	back pain, pain in extremity (leg pain)	tendon pain (tendinitis like symptoms)	
Renal and urinary disorders			
Uncommon		renal impairment including acute renal failure	micturition disorder, pollakiuria
Rare	nocturia		
Reproductive system and breast disorders			
Uncommon	erectile		gynaecomastia

	dysfunction		
General disorders and administration site condition			
Common	peripheral oedema		pain
Uncommon	asthenia, chest pain, fatigue, oedema		
Rare	malaise	influenza-like illness	
Investigations			
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased
Rare	blood uric acid increased	blood creatine phosphokinase increased, haemoglobin decreased	

1: the event may be a chance finding or related to a mechanism currently not known

2: most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

3: cases of interstitial lung disease (predominantly interstitial pneumonia and eosinophilic pneumonia) have been reported from post-marketing experience with telmisartan

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both telmisartan and amlodipine.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

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

ATC Code: C09DB04.

TELAM 80/5 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.

TELAM 80/5 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 inh
Telmisartan does not inhibit angiote
bradykinin. Therefore it is not expec
In humans, an 80 mg dose of Tel
pressure increase. The inhibitory effe
After the first dose of Telmisartan, th
3 hours. The maximum reduction i
treatment and is sustained during lon
The antihypertensive effect persists
the next dose as shown by ambulat
ratios consistently above 80 % seen
studies. There is an apparent trend
pressure. In this respect data concern

In patients with hypertension Tel
affecting pulse rate. The contribut
hypotensive activity has still to be de
of substances representative of other
trials comparing telmisartan to amlo

Upon abrupt cessation of treatment v
over a period of several days withou

The incidence of dry cough was sig
angiotensin converting enzyme inh
treatments.

Two large randomised, controlled
with Ramipril Global Endpoint T
Diabetes)) have examined the use
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 non- dihydropyridine 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 despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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 TELAM 80/5 resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

TELAM 80/5 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 <90 mmHg was achieved in 71.6 %, 74.8 %, 82.1 %, 85.3 % of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive

In a subset of 1050 patients with
responded sufficiently to monothera
systolic/diastolic blood pressure w
mmHg with 40 mg/5 mg; −22.5/−1
seen with amlodipine 10 mg (−21.0/
with 40 mg/5 mg; 0.5 % with 80 mg/
Automated ambulatory blood pressu
the results seen with in-clinic systoli
hours dosing period.

In a further multicentre, randomised
patients with mild to severe hyperte
TELAM 80/5 (40 mg/5 mg or 80
treatment, each of the combinations
doses in reducing systolic and diast
mg/5 mg, 80 mg/5 mg versus −6.2/
higher diastolic blood pressure contr
%, 63.8 % with 40 mg/5 mg and 8
Oedema rates were significantly low
(4.4 % versus 24.9 %, respectively).

In another multicentre, randomised,
947 patients with mild to severe hy
received TELAM 80/5 (40 mg/10
treatment, each of the combinatio
monotherapy in reducing diastolic a
40 mg/10 mg, 80 mg/10 mg versus
pressure normalisation rates compare

mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of TELAM 80/5 was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with TELAM 80/5 40 mg/10 mg had additional blood pressure reduction by up-titration to TELAM 80/5 80 mg/10 mg.

The overall incidence of adverse reactions with TELAM 80/5 in the clinical trial programme was low with only 12.7 % of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received TELAM 80/5 as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with TELAM 80/5 40 mg/5 mg and 80 mg/5 mg, 8.8 % with TELAM 80/5 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 TELAM 80/5 was similar irrespective of age and gender, and was similar in patients with and without diabetes.

TELAM 80/5 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 TELAM 80/5 in all subsets of the paediatric population in hypertension

5.2 Pharmacokinetic Properties

Pharmacokinetic of the fixed dose combination

The rate and extent of absorption of TELAM 80/5 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.

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.

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.

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. Cumulative urinary excretion is <1 % of dose. Total plasma clearance

(Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min). 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 for 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.

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 Preclinical safety Data

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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. 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 10 times the maximum recommended human dose of 10 mg/day on an mg/m2 basis).

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol, Meglumine, Potassium Hydroxide, Purified Water, Methylene Chloride, Kyron T-314, Purified Talc, Sodium Starch Glycolate (Primojel). Colloidal Anhydrous Silica, Magnesium Stearate, Dibasic Calcium Phosphate, Maize Starch, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Col. Ponceau 4R BIS (SUPRA), Croscarmellose Sodium (Primellose).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C & Protect from light.

6.5 Nature and contents of container

Alu/Alu Blister of 10 tablets Such 3 Blisters are packed in packed in a printed carton with leaflet inside.

7. Marketing Authorization Holder

BIO-GENERICS NIGERIA LIMITED,
13, HUGHES AVENUE, ALAGOMEJI,
YABA, LAGOS STATE.