TELMISARTAN 40mg & AMLODIPINE 5 mg TABLETS

ARBITEL- AM

13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
Telmisartan & Amlodipine

13.1 Strength:
40/5

13.2 Pharmaceutical form
Tablets for oral administration

14. Quality and Quantitative Composition
Each film coated tablet contains:
Telmisartan BP…….40 mg
Amlodipine Besilate BP equivalent to Amlodipine……..…. 5mg

15. Pharmaceutical Form
Tablets

16. Clinical Particulars
16.1 Therapeutic indications
Treatment of essential hypertension in adults:
Add on therapy
Telmisartan & Amlodipine 40 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.

16.2 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
Telmisartan & Amlodipine 80 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled on Telmisartan & Amlodipine 40 mg/10 mg or Telmisartan & Amlodipine 80 mg/5 mg.
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 Telmisartan & Amlodipine 40 mg/5 mg 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 Telmisartan & Amlodipine containing the same component doses in one tablet once daily.

Special population

Elderly patients (> 65 years)

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

Patients with renal impairment

Limited experience is available in patients with severe renal impairment or hemodialysis. 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.

Patients with hepatic impairment

Telmisartan & Amlodipine is contraindicated in patients with severe hepatic impairment.

In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily.

Paediatric population

The safety and efficacy of telmisartan/amlodipine in children aged below 18 years have not been established. No data are available.

16.3 Method of administration

Oral use

Telmisartan & Amlodipine can be taken with or without food. It is recommended to take Telmisartan & Amlodipine with some liquid.

16.4 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan/amlodipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

16.5 Special warning and precautions

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. 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.

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 dialyzable.

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, immunosuppressive (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.

Sorbitol

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

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.

16.6 Paediatric population

None

16.7 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 antihypertensive 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. spironolactone, 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 hypocalcaemia, 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 AUC_{0-24} and C_{max} 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

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, *Hypericum perforatum*) may lead to a lower plasma concentration of amlodipine.

Grapefruit and grapefruit juice

Concomitant administration of 240 ml of grapefruit 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, and simethicone), cimetidine, antibiotics and oral hypoglycemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

16.8 Additional information on special populations

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic 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.

16.9 Paediatric population

None

16.10 Fertility, pregnancy and lactation

16.10.1 General principles

16.10.2 Women of childbearing potential / Contraception in males and females

Not known

16.10.3 *Pregnancy*

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, and 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.

16.10.4 ***Lactation***

Because no information is available regarding the use of telmisartan and/or amlodipine 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.

16.4.5 ***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.

16.11 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.

16.12 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 Telmisartan & Amlodipine 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 Telmisartan & Amlodipine has been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of whom 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 (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Telmisartan & Amlodipine**	**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			mood change
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			vasculitic
Respiratory, thoracic and mediastinal disorders			
Uncommon	cough	Dyspnoea	Dyspnoea, rhinitis
Very rare	interstitial lung disease[3]		
Gastrointestinal disorder			
Uncommon	abdominal pain, diarrhoea, nausea	flatulence	change of bowel habit
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 discolorations, 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

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 dysfunction		gynaecomastia
General disorders and administration site condition			
Common	peripheral oedema		
Uncommon	asthenia, chest pain, fatigue, oedema		pain
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

16.13 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 hemodialysis.

17. Pharmacological Properties

17.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.
Telmisartan & Amlodipine combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridine 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 & Amlodipine 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 AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterized 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 effects.
In human, 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.

Treatment of essential hypertension

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 (SBP). In this respect data concerning diastolic blood pressure (DBP) 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 agents' 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.

Amlodipine

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

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

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (after load) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

17.2 Pharmacokinetic Properties:

Pharmacokinetic of the fixed dose combination

The rate and extent of absorption of Telmisartan & Amlodipine 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 ($AUC_{0-\infty}$) 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 (V_{dss}) 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 (approximately 90 %) metabolised by the liver to inactive metabolites.

Elimination

Telmisartan is characterized by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) 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 (Cl_{tot}) 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. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.
Amlodipine exhibits linear pharmacokinetics.

Special populations

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 C_{max} 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.

17.3 Preclinical safety Data

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 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's 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 with Amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a 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.

17.4 Environmental Risk Assessment (ERA)

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

18. Pharmaceutical Particulars

18.1 List of excipients

Mannitol CD, Cross povidone, Betadex, Sodium lauryl sulphate, Povidone, Methylene chloride, Microcrystalline cellulose, Magnesium Stearate, HPMC 15 CPS, Titanium Dioxide, Talc, Polysorbate-80, Propylene Glycol, Tartrazine Lake-Coloring agent.

18.2 Incompatibilities

None

18.3 Shelf life

36 months from the date of manufacturing.

18.4 Special precautions for storage

Store below 30°C. Keep this medicine out of reach of children

18.5 Nature and contents of container

Alu/Alu Blister pack of 10 Tablets, such 3 blisters are packed in carton along with pack insert.

18.6 Special precautions for disposal and other handling

None

19. Marketing Authorization Holder and Manufacturing Site Addresses

MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur - 635 126 (T.N.)
INDIA

20. Marketing Authorisation Number

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21. Date of First Registration/Renewal of the registration

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22. Date of revision of the text
April 2019

23. DOSIMETRY
Not applicable

24. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Not applicable