1. NAME OF THE MEDICINAL PRODUCT

AMLOTEL 5mg + 40mg Tablets
AMLOTEL10mg + 40mg Tablets
AMLOTEL 5mg + 80mg Tablets
AMLOTEL 10mg + 80mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLOTEL 5mg + 40mg Tablets:
Each uncoated tablets contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besylate).
AMLOTEL 10mg + 40mg Tablets:
Each uncoated tablets contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besylate).
AMLOTEL 5mg + 80mg Tablets:
Each uncoated tablets contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besylate).
AMLOTEL 10mg + 80mg Tablets:
Each uncoated tablets contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

The tablets are for oral administration.

AMLOTEL 5mg + 40mg Tablets:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L389'.

AMLOTEL 10mg + 40mg Tablets:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer de bossed with 'L390'

AMLOTEL 5mg + 80mg Tablets:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer de bossed with 'L391'

AMLOTEL 10mg +80mg Tablets:
Oval shaped biconvex, Bilayer, uncoated tablets with one white to off white color layer and one blue color mottled layer debossed with 'L388'

4. CLINICAL PARTICULARS

4.1 Indications

Treatment of essential hypertension in adults.

Replacement Therapy

Patients receiving telmisartan and amlodipine from separate tablets may instead receive AMLOTEL containing the same component doses.

Add on therapy
AMLOTEL is indicated in patients whose blood pressure is not adequately controlled on telmisartan or amlodipine monotherapy.

Initial therapy
AMLOTEL may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of AMLOTEL tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of AMLOTEL tablets.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as stroke, heart attacks and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. Consider the patient's baseline blood pressure, the target goals and the incremental likelihood of achieving goals with a combination compared to monotherapy when deciding whether to use AMLOTEL tablets as initial therapy. Individual blood pressure goals may vary based upon the patient'srisk.

4.2 Dosage andAdministration

DOSAGE

Adults
AMLOTEL should be taken once daily. The maximum recommendation dose is AMLOTEL 80mg/10mg one tablet per day.

Replacement Therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive AMLOTEL containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance.

Add on therapy
AMLOTEL may be administered in patients whose blood pressure is not adequately controlled with amlodipine or telmisartan alone.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to AMLOTEL 40/5mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

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

Initial therapy
A patient may be initiated on AMLOTEL if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of AMLOTEL is 40/5 mg once daily. Patients requiring larger blood pressure reductions may be started on AMLOTEL 80/5 mg once daily.

If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80/10 mg once daily.

Initial therapy with AMLOTEL is not recommended in patients ≥ 75 years old or with hepatic impairment. Correct imbalances on intravascular volume- or salt-depletion, before initiating therapy with AMLOTEL tablets.

AMLOTEL can be administered with other antihypertensive drugs.

Special populations

Geriatric patients
No dose adjustment is necessary for geriatric patients. Little information is available in the very elderly patients. Normal amlodipine dosage regimens are recommended in the elderly, but increase of dosage should take place with care.

Paediatric patients
AMLOTEL is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Renal impairment

No posology adjustment is required for patients with renal impairment, including those on haemodialysis. Limited experience is available with severe renal impairment or haemodialysis. Caution is advised when using AMLOTEL in such patients as amlodipine and telmisartan are not dialysable. Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable

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

Method of administration
AMLOTEL tablets are for once-daily oral administration and should be swallowed whole with liquid. AMLOTEL can be taken with or without food.

Handling Instructions

Due to the hygroscopic property of the tablets they should be taken out of the sealed blister shortly before administration.

4.3 Contraindications

- Hypersensitivity to the active substances, or to any of the excipients
- Hypersensitivity to dihydropyridine derivatives
- Second and third trimesters of pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- Severe hypotension
- 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 AMLOTEL with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated.

4.4 Special Warnings and Precautions

Pregnancy:
Angiotensin II receptor blockers should not be initiated during pregnancy.
Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and if appropriate, alternative therapy should be started.

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, extend trauma).

Serum potassium should be monitored closely in these patients.

Volume and/or sodium depleted patients:
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 AMLOTEL.

Hepatic impairment:
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance.
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose.

AMLOTEL 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.

Renal impairment and kidney transplant:
When AMLOTEL 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 AMLOTEL in patients with a recent kidney transplant.

Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

Dual blockade of the renin-angiotensin-aldosterone system:
As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. AMLOTEL can be administered with other antihypertensive drugs, however dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor antagonist) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function.

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 AMLOTEL in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with cardiac failure

In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Diabetes mellitus:
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with AMLOTEL.

Geriatric patients
The increase of the amlodipine dosage should take place with care in the geriatric patients.

Ethnic differences:
AMLOTEL was effective when treating black patients (usually a low-renin population).

Ischaemic heart disease:
As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Fertility, Pregnancy and Lactation

The effects of AMLOTEL during pregnancy and lactation are not known. Effects related to the mono components are described below.

Pregnancy

Telmisartan:
The use of angiotensin II receptor blocker is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.
Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

The use of angiotensin II receptor blockers is contraindicated during the second and third trimester of pregnancy. Angiotensin II receptor blocker exposure 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 blocker 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 blocker should be closely observed for hypotension.

Amlodipine:
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

Lactation

AMLOTEL is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk.
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 of the potential adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of this therapy for the mother .

Fertility

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed.
Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.

In non-clinical studies, no effects of telmisartan on male and female fertility were observed.

In some patients treated by calcium channel blockers, reversible biochemical changes in the head of spermatozoa have been reported.
Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.6 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that syncope, somnolence, dizziness or vertigo may occasionally occur when taking antihypertensive therapy. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.7 Adverse Reactions

Summary of the safety profile
The safety and tolerability of combination of Telmisartan and Amlodipine has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

No additional adverse reactions were identified in clinical trials with the combination telmisartan plus amlodipine compared to the adverse reactions of the monocomponents. Peripheral oedema, a recognised dose dependent adverse reaction of the monocomponent amlodipine, was generally observed at a lower incidence in patients who received the telmisartan/amlodipine combination than in those who received amlodipine alone.

Adverse reactions previously reported with one of the monocomponents (telmisartan or amlodipine) may be potential adverse reactions with AMLOTEL as well, even if not observed in clinical trials or during the post-marketing period. Therefore in addition to the reported adverse reactions during the combination of Telmisartan and Amlodipine development programme all adverse reactions reported in patients who received telmisartan or amlodipine monotherapy, have been listed for combination of Telmisartan and Amlodipine.

Tabulated summary of adverse reactions
The following adverse reactions derived from the use of the telmisartan/amlodipine combination or the use of the monocomponents (telmisartan or amlodipine) in clinical trials or from post-marketing experience are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms.

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	AMLOTEL	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			leukopenia, thrombocytopenia
Immune system disorders:			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
Metabolism and nutrition disorders:			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in diabetic patients), hyponatraemia	
Very rare			hyperglycaemia
Psychiatric disorders:			
Uncommon		depression, insomnia	depression, anxiety, insomnia, mood altered
Rare	depression, anxiety, insomnia	anxiety	confusional state
Nervous system disorders:			
Common	dizziness		somnolence, dizziness, headache
Uncommon	somnolence, migraine, headache, paraesthesia	syncope (faint)	syncope (faint), paraesthesia, hypoaesthesia, dysgeusia, tremor
Rare	syncope (faint), neuropathy peripheral, hypoaesthesia, dysgeusia, tremor		
Very rare			hypertonia, neuropathy peripheral
Not known			extrapyramidal disorder

Eye disorders:			
Common			visual impairment, diplopia
Rare		visual impairment	
Ear and labyrinth disorders:			
Uncommon	vertigo	vertigo	tinnitus
Cardiac disorders:			
Common			palpitations
Uncommon	bradycardia, palpitations	bradycardia	ventricular tachycardia, arrhythmia, atrial fibrillation, bradycardia
Rare		tachycardia	
Very rare			myocardial infarction
Vascular disorders:			
Common			flushing
Uncommon	hypotension, orthostatic hypotension, flushing	hypotension, orthostatic hypotension	hypotension
Very rare			vasculitis
Respiratory, thoracic and mediastinal disorders:			
Common			dyspnoea
Uncommon	cough	dyspnoea	cough, rhinitis
Gastrointestinal disorders:			
Common			abdominal pain, diarrhoea, dyspepsia, constipation, nausea, change of bowel habit
Uncommon	abdominal pain, diarrhoea, nausea	abdominal pain, diarrhoea, vomiting, dyspepsia, flatulence	vomiting, dry mouth,
Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth	dry mouth, abdominal discomfort	
Very rare			gingival hypertrophy, pancreatitis, gastritis
Hepato-biliary disorders:			
Rare		hepatic function abnormal, liver disorder[2]	
Very rare			hepatitis, jaundice, hepatic enzyme increased (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders:			
Uncommon	pruritus	rash, pruritus, hyperhidrosis	urticaria, rash, pruritus, alopecia, purpura, skin discolouration, hyperhidrosis
Rare	eczema, erythema, rash	angioedema (including fatal outcome),	

		drug eruption, toxic skin eruption, urticaria, eczema, erythema	
Very rare			angioedema, erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome, photosensitivity reaction
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders:			
Common			joint swelling, muscle spasms
Uncommon	arthralgia, back pain, muscle spasms (cramps in legs), myalgia	back pain, muscle spasms, myalgia	arthralgia, back pain, myalgia
Rare	pain in extremity (leg pain)	arthralgia, pain in extremity (leg pain), tendon pain (tendonitis like symptoms)	
Renal and urinary disorders:			
Uncommon		renal impairment including acute renal failure	nocturia, micturition disorder, pollakiuria
Rare	nocturia		
Reproductive system and breast disorders:			
Uncommon	erectile dysfunction		erectile dysfunction, gynaecomastia
General disorders and administration site condition:			
Very common			oedema
Common	oedema peripheral		asthenia, fatigue
Uncommon	asthenia, chest pain, fatigue, oedema	chest pain, asthenia	chest pain, pain, malaise
Rare	malaise	influenza-like illness	
Investigations:			
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased
Rare	blood uric acid increased	hepatic enzymes increased, blood creatine phosphokinase increased, haemoglobin decreased, blood uric acid increased	

[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

4.8 Drug Interactions

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

Interactions linked to the combination

No drugs interaction studies have been performed with AMLOTEL and other medicinal products.

Other antihypertensive agents
The blood pressure lowering effect of AMLOTEL can be increased by concomitant use of other antihypertensive medicinal products.

Agents 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 AMLOTEL, e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Telmisartan may increase the hypotensive effect of other antihypertensive agents.
Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

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.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.
Cases have also been reported with angiotensin II receptor blocker including telmisartan. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (i.e. ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and their renal function should be monitored at the beginning of combined treatment.
A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Interactions linked to amlodipine

Grapefruit and grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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).

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

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.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin
Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Additional information
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.9 Overdose

Symptoms:
There is no experience of overdose with AMLOTEL. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia; bradycardia also occurred. 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 may occur. Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

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. If symptomatic hypotension should occur, supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Telmisartan is not removed from blood by hemofiltration and is not dialyzable. Amlodipine is not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II receptor blocker, plain (telmisartan), combinations with dihydropyridine derivatives (amlodipine),

ATC Code: C09DB04.

Mode of action

AMLOTEL combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor blocker, 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.

AMLOTEL once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan:
Telmisartan is an orally effective and specific angiotensin II receptor (type AT1) blocker. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long lasting.
Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

In man, 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.

Amlodipine:
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion blocker) 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.

Pharmacodynamics

Telmisartan:
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 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 SBP. In this respect data concerning DBP are inconsistent.
In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.
The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan).
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.
Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy .

Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.
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:
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.

5.2 Pharmacokinetics properties

Pharmacokinetics of the fixed dose combination
The rate and extent of absorption of AMLOTEL are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetic of the single components:

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) 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.

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected 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 (Vss) is approximately 500 L.

The volume of distribution of amlodipine is approximately 21 L/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins in hypertensivepatients.

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.
After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, exclusively as unchanged compound. Cumulative urinary excretion is < 2% of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 ml/min compared with hepatic blood flow (about 1500mL/min).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. 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
The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan.

PK in Specific Populations

Paediatric population (age below 18 years)
No pharmacokinetic data for AMLOTEL are available in the paediatric population.

Gender differences

Gender differences in plasma concentrations of telmisartan were observed, C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.

Geriatric patients

The pharmacokinetics of telmisartan do not differ between younger and geriatric patients.
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half- life.

Renal impairment

Lower plasma concentrations of telmisartan 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 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 .

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Sodium Hydroxide, Meglumine, Povidone K-25, Sodium Stearyl Fumarate, Magnesium Stearate, Microcrystalline Cellulose, Corn Starch, Crospovidone XL 10, Iron Oxide Black, FD&C Blue #1 / Brilliant Blue FCFAC 11-13%

6.2 Incompatibilities

Not applicable.

6.3 Nature and contents of container

Blister pack of Aluminium Foil and CFB foil

AMLOTEL 5MG +40MG TABLETS : Blister pack of 14 Tablets. Such 7 Blister is packed in a carton,Blister pack of 14 Tablets. Such 2 Blister is packed in a carton
AMLOTEL 10MG +40MG TABLETS: Blister pack of 14 Tablets. Such 7 Blister is packed in a carton,Blister pack of 14 Tablets. Such 2 Blister is packed in a carton.
AMLOTEL 5MG +80MG TABLETS: Blister pack of 14 Tablets. Such 7 Blister is packed in a carton, Blister pack of 14 Tablets. Such 2 Blister is packed in a carton.
AMLOTEL 10MG +80MG TABLETS: Blister pack of 14 Tablets. Such 2 Blister is packed in a carton, Blister pack of 14 Tablets. Such 7 Blister is packed in a carton.

6.4 Storage conditions

Store below 30ºC. Store in the original package in order to protect from light and moisture.

7. NAME AND ADDRESS OF MANUFACTURER

Manufactured by:
Alembic Pharmaceuticals Limited. Formulation Division,
Village Panelav, P.O. Tajpura, Near Baska, Taluka Halol,
Panchmahal, Gujarat – 389350 India.

Product Registration Holder
GENPHARMA SDN. BHD.
Lot 5016, Jalan Teratai,
5 ½ Mile Off Jalan Meru,
41050 Klang, Selangor, Malaysia

Date of revision: 16/06/2025

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