APPROVED PROFESSIONAL INFORMATION
DR. REDDY'S LABORATORIES (PTY) LTD
TESAMOLOT™ 40/5; 40/10; 80/5; 80/10

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

TESAMOLOT™ 40/5 tablet

TESAMOLOT™ 40/10 tablet

TESAMOLOT™ 80/5 tablet

TESAMOLOT™ 80/10 tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TESAMOLOT™ 40/5: Each tablet contains 40 mg telmisartan and 5 mg amlodipine base (as besilate salt).

Excipient(s) with known effect: Contains sugar (mannitol).

Contains approximately 351,605 mg sugar (mannitol) per tablet.

TESAMOLOT ™ 40/10: Each tablet contains 40 mg telmisartan and 10 mg amlodipine base (as besilate salt).

Excipient(s) with known effect: Contains sugar (mannitol).

Contains approximately 344,67 mg sugar (mannitol) per tablet.

TESAMOLOT™ 80/5: Each tablet contains 80 mg telmisartan and 5 mg amlodipine base (as besilate salt).

Excipient(s) with known effect: Contains sugar (mannitol).

Contains approximately 519,945 mg sugar (mannitol) per tablet.

TESAMOLOT™ 80/10: Each tablet contains 80 mg telmisartan and 10 mg amlodipine base (as besilate salt).

Excipient(s) with known effect: Contains sugar (mannitol).

Contains approximately 513,01 mg sugar (mannitol) per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

TESAMOLOT™ 40/5: Oblong shaped, uncoated, biconvex, bilayered tablet with off white to white layer on one side and pale pink to pink layer with mottled appearance on the other side.

TESAMOLOT™ 40/10: Oblong shaped, uncoated, biconvex, bilayered tablet with off white to white layer on one side and pale yellow to yellow layer on the other side.

TESAMOLOT™ 80/5: Oblong shaped, uncoated, biconvex, bilayered tablet with off white to white layer on one side and pale pink to pink layer with mottled appearance on the other side.

TESAMOLOT™ 80/10: Oblong shaped, uncoated, biconvex, bilayered tablet with off white to white layer on one side and pale yellow to yellow layer the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy:

Treatment of essential hypertension in patients who have been stabilised on the two component medicines used at the same dose.

Add on therapy:

TESAMOLOT**™** is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet once daily.

Replacement therapy:

Patients taking telmisartan and amlodipine as separate tablets can instead take TESAMOLOT™ containing the same component doses in one tablet once daily.

Add on therapy:

TESAMOLOT™ may be administered in patients whose blood pressure is not adequately controlled amlodipine alone. The usual starting TESAMOLOT™ is 40/5 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.

Special populations:

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment (see Section 4.4).

Amlodipine and telmisartan are not dialysable.

Hepatic impairment

In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the dose should not exceed 40/5 mg or 40/10 mg once daily.

TESAMOLOT™ is contraindicated in patients with severe hepatic impairment (see Section 4.3).

Elderly (> 65 years)

No dose adjustment is necessary for elderly patients.

Children and adolescents (< 18 years old)

TESAMOLOT™ is not recommended in children aged below 18 years, due to a lack of safety and efficacy studies.

Method of administration

TESAMOLOT™ is for oral administration. It is recommended to take TESAMOLOT™ with some liquid, with or without food.

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 (see Section 4.5).

4.3 Contraindications

TESAMOLOT™ is contraindicated in:

- Patients who have a known hypersensitivity to telmisartan and/ or amlodipine or to the other excipients of TESAMOLOT™ (see Section 6.1).
- Patients who have a hypersensitivity to dihydropyridine derivatives.
- Patients with a history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Patients being treated concomitantly with fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.
- Patients with hereditary or idiopathic angioedema.
- Patients with Hypertrophic Obstructive Cardiomyopathy (HOCM).
- Patients with severe renal function impairment (creatinine clearance less than 30 ml/min).
- Patients with bilateral renal artery stenosis.
- Patients with a single kidney with renal artery stenosis.
- Patients with aortic stenosis.
- Patients with concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride (see Section 4.4).
- Patients on lithium therapy: concomitant administration with TESAMOLOT may lead to toxic blood concentrations of lithium (see Section 4.5).
- Patients being treated concomitantly with aliskiren-containing medicines (see Sections 4.4 & 4.5).
- Patients with porphyria.
- Patients with biliary obstructive disorders.
- Patients with severe hepatic impairment (see Section 4.4).
- Patients suffering from cardiogenic shock.
- Pregnancy and lactation [women who are or may potentially be pregnant and women who are or planning to breast feed (see Section 4.6)].

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving TESAMOLOT™, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine.

(See Sections 4.3 & 4.6).

Pregnancy:

TESAMOLOT™ should not be initiated during pregnancy (see Section 4.3). 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 TESAMOLOT**™** should be stopped immediately, and, if appropriate, alternative therapy should be started (see Section 4.6).

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 contraindicated.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hepatic impairment:

Telmisartan (ingredient of TESAMOLOT™ 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's (ingredient of-TESAMOLOT™) half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. TESAMOLOT™ should therefore be used with caution in patients with mild to moderate impairment of liver function and should not be used in patients with severe liver impairment (see Section 4.3).

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 medicines that affect the renin-angiotensin-aldosterone system (RAAS) (see Section 4.3).

Renal impairment and kidney transplant:

When TESAMOLOT™ 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 TESAMOLOT™ 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 TESAMOLOT™. If hypotension occurs with TESAMOLOT™, 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 stabilised.

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 medicines 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 medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of TESAMOLOT™ is not recommended.

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See Section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzymes (ACE) inhibitors/Angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

TESAMOLOT™ is contraindicated 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 TESAMOLOT™ 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.

Hyperkalaemia:

During treatment with TESAMOLOT™ hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicines that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with TESAMOLOT™.

Diabetic patients treated with insulin or antidiabetics:

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 medicines 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 TESAMOLOT™.

Other:

Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Important information about some of the excipients of TESAMOLOT™:

TESAMOLOT™ contains mannitol. May have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

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

Interactions common to the combination:

No medicine interaction studies have been performed with TESAMOLOT™ and other medicines.

Concomitant use to be taken into account:

Other antihypertensive medicines:

The blood pressure lowering effect of TESAMOLOT™ can be increased by concomitant use of other antihypertensive medicines.

Medicines with blood pressure lowering potential:

Based on their pharmacological properties it can be expected that the following medicines may potentiate the hypotensive effects of all antihypertensives including TESAMOLOT™, e.g., baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

Corticosteroids (systemic route):

Reduction of the antihypertensive effect.

Interactions linked to the telmisartan component of TESAMOLOT™:

Telmisartan may increase the hypotensive effect of other antihypertensive medicines. Other interactions of clinical significance have not been identified.

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 (ACE) inhibitors. Increased serum levels have also been reported with telmisartan.

Treatment with NSAIDs (i.e., aspirin 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 TESAMOLOT™ should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive medicines like TESAMOLOT™ by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of angiotensin-converting enzyme (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 (see Sections 4.3 & 4.4).

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see Section 4.3).

Interactions linked to the amlodipine component of TESAMOLOT™:

Concomitant use requiring caution:

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.

CYP3A4 inhibitors:

A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50 % and the effect of amlodipine is increased).

The possibility that more potent inhibitors of CYP3A4 (i.e., ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant medicines (e.g., carbamazepine, phenobarbitone, phenytoin, fosphenytoin,

primidone) rifampicin, Hypericum perforatum):

Concomitant use may lead to a lower plasma concentration of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

Concomitant use to be taken into account:

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.

Immunosuppressants:

Amlodipine may increase the systemic exposure of ciclosporin or tacrolimus when co-administered. Frequent monitoring of trough blood levels of ciclosporin and tacrolimus and dose adjustment when appropriate is recommended.

Others:

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic medicines. When amlodipine and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Additional information:

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.

Co-administration of amlodipine with cimetidine had no significant effect on the pharmacokinetics of amlodipine.

Co-administration of amlodipine with atorvastatin, digoxin or warfarin had no significant effect on the pharmacokinetics or pharmacodynamics of these medicines.

4.6 Fertility, pregnancy and lactation

TESAMOLOT™ should not be used during pregnancy and lactation.

Effects relating to the monotherapy components are described below.

Pregnancy:

Telmisartan:

Safety in pregnancy and lactation has not been established. When pregnancy is planned or confirmed, TESAMOLOT™ should be discontinued as soon as possible (see Section 4.3 & 4.4).

Medicines affecting the renin-angiotensin system, such as TESAMOLOT™, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

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 TESAMOLOT™ should be stopped immediately, and, if appropriate, alternative therapy should be started.

Should exposure to TESAMOLOT™ have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken TESAMOLOT™ should be closely observed for hypotension.

Lactation:

It is not known whether telmisartan (as in TESAMOLOT™) is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. Amlodipine has been identified in breastfed infants of treated women. The effect of amlodipine on infants is unknown. Because of the potential adverse reactions in breastfed infants, TESAMOLOT™ should not be used by breastfeeding mothers (see Section 4.3).

4.7 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, patients should be advised that they may experience undesirable effects such as syncope (fainting), somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a vehicle or operating machinery. If patients experience these adverse effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Infections and infestations

- *Less frequent*: cystitis.

Psychiatric disorders

- *Less frequent:* depression, anxiety, insomnia.

Nervous system disorders

- *Frequent:* dizziness.
- *Less frequent:* somnolence, migraine, headache, paraesthesia, syncope (fainting), peripheral neuropathy, hypoaesthesia, dysgeusia, tremor.

Ear and labyrinth disorders

- *Less frequent:* vertigo.

Cardiac disorders

- *Less frequent:* bradycardia, palpitations.

Vascular disorders

- *Less frequent*: hypotension, orthostatic hypotension, flushing.

Respiratory, thoracic and mediastinal disorders

- *Less frequent:* cough.

Gastrointestinal disorders

- *Less frequent:* abdominal pain, diarrhoea, nausea, vomiting, gingival hypertrophy, dyspepsia, dry mouth.

Skin and subcutaneous tissue disorders

- *Less frequent:* pruritus, eczema, erythema, rash.

Musculoskeletal and connective tissue disorders

- *Less frequent:* arthralgia, muscle spasms, myalgia, back pain, pain in extremity.

Renal and urinary disorders

- *Less frequent:* nocturia.

Reproductive system and breast disorders:

- *Less frequent:* erectile dysfunction.

General disorders and administration site conditions

- *Less frequent:* peripheral oedema, asthenia, chest pain, fatigue, oedema, malaise.

Investigations

- *Less frequent:* increased hepatic enzymes, increased blood uric acid.

The following side-effects have been observed and reported during treatment with telmisartan monotherapy:

Infections and infestations

- *Frequent*: sepsis including fatal outcome, urinary tract infections including cystitis, upper respiratory tract infections including pharyngitis and sinusitis.

Blood and lymphatic system disorders

- *Less frequent:* anaemia, eosinophilia, thrombocytopenia.

Immune system disorders

- *Less frequent:* angioedema, anaphylactic reaction, hypersensitivity.

Metabolism and nutrition disorders

- *Less frequent:* hyperkalaemia, hypoglycaemia (in diabetic patients).

Eye disorders

- *Less frequent:* visual disturbance.

Cardiac disorders

- *Less frequent:* tachycardia.

Respiratory, thoracic and mediastinal disorders

- *Less frequent:* dyspnoea.

Gastrointestinal disorders

- *Less frequent:* flatulence, stomach discomfort.

Hepatobiliary disorders

- *Less frequent:* abnormal hepatic function, liver disorder.

Skin and subcutaneous tissue disorders

- *Less frequent:* hyperhidrosis, urticaria, drug eruption, toxic skin eruption, angioedema.

Musculoskeletal and connective tissue disorders

- *Less frequent:* tendon pain (tendinitis like symptoms).

Renal and urinary disorders

- *Less frequent:* renal impairment including acute renal failure.

General disorders and administration site conditions

- *Less frequent:* influenza-like illness.

Investigations

- *Less frequent:* haemoglobin decreased, blood creatinine increased, blood creatinine phosphokinase (CPK) increased.

The following side-effects have been observed and reported during treatment with amlodipine monotherapy:

Blood and lymphatic system disorders

- *Less frequent:* thrombocytopenia, leukocytopenia.

Immune system disorders

- *Less frequent:* hypersensitivity.

Metabolism and nutrition disorders

- *Less frequent:* hyperglycaemia.

Psychiatric disorders

- *Less frequent:* mood change, confusion.

Nervous system disorders

- *Less frequent:* extrapyramidal syndrome.

Eye disorders

- *Less frequent:* visual impairment.

Ear and labyrinth disorders

- *Less frequent:* tinnitus.

Cardiac disorders

- *Less frequent:* myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation.

Vascular disorders

- *Less frequent:* vasculitis.

Respiratory, thoracic and mediastinal disorders

- *Less frequent:* dyspnoea, rhinitis.

Gastrointestinal disorders

- *Less frequent:* change of bowel habits, pancreatitis, gastritis.

Hepatobiliary disorders

- *Less frequent:* hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis).

Skin and subcutaneous tissue disorders

- *Less frequent:* hyperhidrosis, urticaria, alopecia, purpura, skin discolouration, erythema multiforme, angioedema, exfoliative dermatitis, Steven-Johnson Syndrome, photosensitivity.

Renal and urinary disorders

- *Less frequent:* micturition disorder, pollakiuria.

Reproductive system and breast disorders

- *Less frequent:* gynaecomastia.

General disorders and administration site conditions

- *Less frequent:* pain, weight increase, weight decrease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms:

TESAMOLOT™: There is no experience of overdose. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.

Telmisartan:

The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Amlodipine:

Available data for amlodipine suggest that gross overdosage could 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.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24 to 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Therapy:

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

Pharmacological classification: A 7.1.3 Vascular medicines – other hypotensives

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

5.1 Pharmacodynamic properties

Mechanism of action

TESAMOLOT™ combines two antihypertensive compounds with complementary mechanisms of actions: telmisartan- an angiotensin II receptor antagonist and amlodipine - a dihydropyridinic calcium channel blocker. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

TESAMOLOT™ 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 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 monotherapy does not inhibit human plasma renin or block ion channels.

Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, an 80 mg dose of telmisartan monotherapy almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies.

There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

<u>Amlodipine:</u>

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.

Telmisartan/Amlodipine:

Treatment with each combination dose of TESAMOLOT™ resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy.

The antihypertensive effect of TESAMOLOT™ was similar, irrespective of age and gender and was similar in patients with and without diabetes.

TESAMOLOT™ has not been studied in any patient population other than hypertension.

5.2 Pharmacokinetics properties

Pharmacokinetic properties of the fixed dose combination:

The rate and extent of absorption of TESAMOLOT™ 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 to 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.

Metabolism*:*

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 (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 to 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.

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 to 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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ferric oxide red

Ferric oxide yellow

Magnesium stearate

Meglumine

Polysorbate 80

Povidone

Purified water

Sodium hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

TESAMOLOT™ tablets are packed in Alu-Alu blisters in pack size of 28.

6.6 Special precautions for disposal <and other handling>

Any unused medicine or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

TESAMOLOT™ 40/5: 53/7.1.3/0250

TESAMOLOT™ 40/10: 53/7.1.3/0251

TESAMOLOT™ 80/5: 53/7.1.3/0252

TESAMOLOT™ 80/10: 53/7.1.3/0253

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 February 2023

10 DATE OF REVISION OF THE TEXT

21 April 2023