PROFESSIONAL INFORMATION

TESDYN RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TESDYN 40/5 mg tablet

TESDYN 40/10 mg tablet

TESDYN 80/5 mg tablet

TESDYN 80/10 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TESDYN 40/5 mg: Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besylate). TESDYN 40/5 mg contains sugar alcohol – mannitol 169,94 mg/tablet.

TESDYN 40/10 mg: Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besylate). TESDYN 40/10 mg contains sugar alcohol – mannitol 169,94 mg/tablet**.**

TESDYN 80/5 mg: Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besylate). TESDYN 80/5 mg contains sugar alcohol – mannitol 339,88 mg/tablet.

TESDYN 80/10 mg: Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besylate). TESDYN 80/5 mg contains sugar alcohol – mannitol 339,88 mg/tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

TESDYN 40/5 mg: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L389’.

TESDYN 40/10 mg: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L390’.

TESDYN 80/5 mg: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L391’.

TESDYN 80/10 mg: Oval shaped biconvex, bilayer, uncoated tablets with one white to off white colour layer and one blue colour mottled layer debossed with ‘L388’.

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:

TESDYN is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

4.2 Posology and method of administration

Posology:

Adults:

TESDYN should be taken once a day.

Replacement therapy:

Patients currently taking telmisartan and amlodipine as separate tablets can take TESDYN containing the same component doses in one tablet, once a day.

Add on therapy:

TESDYN may be administered to patients whose blood pressure is not adequately controlled with amlodipine alone.

The usual starting dose of TESDYN 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:

TESDYN is to be administered with caution in patients with mild to moderate hepatic impairment. For telmisartan, the dose should not exceed a daily dose of 40/5 mg or 40/10 mg.

Elderly:

No dose adjustment is required in elderly patients.

Paediatric population:

TESDYN is not recommended for use in children and adolescents under the age of 18 due to lack of data on safety and efficacy.

Method of administration

Tablet for oral administration.

TESDYN can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to telmisartan, amlodipine, dihydropyridine derivatives or to any of the ingredients of TESDYN listed in section 6.1.
- 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.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).

- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (section 4.4).
- Porphyria.
- Lithium therapy: Concomitant administration with TESDYN may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of TESDYN with aliskiren-containing products is contra-indicated (see sections 4.4 and 4.5).
- Biliary obstructive disorders.
- Severe hepatic impairment.
- Cardiogenic shock.
- Concomitant use of fluoroquinolones with 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.

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking TESDYN, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors,

angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of TESDYN and aliskiren is therefore contra-indicated (see section 4.3). TESDYN should not be used concomitantly with aliskiren (see section 4.3).

Hepatic impairment:

Telmisartan (as contained in TESDYN) is mostly eliminated in the bile, therefore, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. TESDYN 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 (see section 4.3).

Renal impairment and kidney transplant:

Periodic monitoring of potassium and creatinine serum levels is recommended when TESDYN is used in patients with impaired renal function. There is no experience regarding the administration of TESDYN in patients with a recent kidney transplant. Telmisartan and amlodipine (as in TESDYN) 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. These conditions require correction prior the administration of TESDYN.

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 TESDYN, that affects this system, has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

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.

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 TESDYN is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy:

TESDYN is contraindicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction:

There are no data to support the use of TESDYN 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:

Hyperkalaemia may occur during treatment with TESDYN, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience during administration of medicines that affect the renin-angiotensin system, concomitant use of TESDYN with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase the potassium level (heparin, etc.), an increase in serum potassium may occur. Coadministration of these medicines with TESDYN should be done with caution.

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 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 TESDYN.

Other:

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

4.5 Interaction with other medicines and other forms of interaction

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

Interactions common to the combination:

No interaction studies have been performed with TESDYN and other medicines.

Concomitant use contraindicated:

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 and 4.4).

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers 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).

Concomitant use to be taken into account:

Other antihypertensive medicines:

The blood pressure lowering effect of TESDYN 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 TESDYN: 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 the telmisartan component of TESDYN:

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

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements:

Angiotensin II receptor antagonists such as telmisartan, as in TESDYN, 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 hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin-converting enzyme (ACE) inhibitors. Increased serum levels have also been reported with telmisartan.

Concomitant use requiring caution

Non-steroidal anti-inflammatory drugs (NSAIDs):

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. Medicines acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and TESDYN should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.
A reduced effect of antihypertensive medicines like TESDYN by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

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:

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.

Co-administration of telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine.

Interactions linked to the amlodipine component of TESDYN:

Concomitant use requiring caution:

Grapefruit and grapefruit juice:

Administration of TESDYN 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:

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, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum):

Co-administration may lead to reduced plasma concentrations 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, limit the dose of simvastatin in patients on amlodipine 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 nitro-glycerine, 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

Women of childbearing potential

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.

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

When pregnancy is planned or confirmed, TESDYN should be discontinued. Medicines affecting the renin-angiotensin system, such as TESDYN, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

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

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

Breastfeeding

Safety in lactation has not been established (see section 4.3).

It is not known whether telmisartan, as in TESDYN, 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, TESDYN should not be used by breastfeeding mothers.

Fertility

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

4.7 Effects on ability to drive and use machines:

TESDYN has moderate influence on the ability to drive and use machines.

Patients should be advised that they may experience undesirable effects such as syncope (fainting), somnolence, dizziness, or vertigo during treatment. Therefore, caution is 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

a). Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur. Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with TESDYN as well, even if not observed in clinical trials or during the post-marketing period.

b). Tabulated summary of adverse reactions – TESDYN

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Cystitis
Psychiatric disorders	Less frequent	Depression, anxiety, insomnia
Nervous system disorders	Frequent Less frequent	Dizziness 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	Frequent Less frequent	Cough Interstitial lung disease
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, connective tissue and bone 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 administrative site conditions	Frequent Less frequent	Peripheral oedema Asthenia, chest pain, fatigue, oedema, malaise
Investigations	Less frequent	hepatic enzymes increased, blood uric acid increased

c). Tabulated summary of adverse reactions – Telmisartan monotherapy

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Urinary tract infections, upper respiratory tract infections including pharyngitis and sinusitis, sepsis (including fatal outcome)
Blood and lymphatic system disorders	Less frequent	Anaemia, eosinophilia, thrombocytopenia

Immune system disorders	Less frequent	Angioedema (with fatal outcome), 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, bradycardia, palpitations
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Less frequent	Flatulence, stomach discomfort
Hepato-biliary disorders	Less frequent	Hepatic function abnormal, liver disorder
Skin and subcutaneous tissue disorders	Less frequent	Hyperhidrosis, urticaria, drug eruption, toxic skin eruption
Musculoskeletal, connective tissue and bone disorders	Less frequent	Tendon pain
Renal and urinary disorders	Less frequent	Renal impairment including acute renal failure
General disorders and administrative site conditions	Less frequent	Influenza-like illness

Investigations	Less frequent	Blood creatinine increased, haemoglobin decreased, blood creatine phosphokinase (CPK) increased

d). Tabulated summary of adverse reactions – Amlodipine monotherapy

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequency unknown	Leucopenia, thrombocytopenia
Immune system disorders	Frequency unknown	Angioedema, hypersensitivity
Metabolism and nutrition disorders	Frequency unknown	Hyperglycaemia
Psychiatric disorders	Frequency unknown	Mood change, confusional state
Nervous system disorders	Frequency unknown	Extrapyramidal disorder, hypertonia
Eye disorders	Frequent Frequency unknown	Visual disturbance (including diploplia) Visual impairment
Ear and labyrinth disorders	Frequency unknown	Tinnitus

Cardiac disorders	Less frequent	Myocardial infarction, dysrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders	Less frequent	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea, rhinitis
Gastrointestinal disorders	Frequency unknown	Change of bowel habit, pancreatitis, gastritis
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	Frequency unknown	Hyperhidrosis, urticaria, alopecia, purpura, skin discolouration, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity reaction, Toxic Epidermal Necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders	Frequent	Ankle swelling
Renal and urinary disorders	Frequency unknown	Micturition disorder, pollakiuria

Reproductive system and breast disorders	Frequency unknown	Gynaecomastia
General disorders and administrative site conditions	Frequency unknown	Pain, weight increased, weight decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

Signs and symptoms:

There is no experience of overdose with TESDYN. 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 might also occur.

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.

Management of overdose:

Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine are not removed

by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: C09DB04.

Pharmacological classification: A 7.1.3 Vascular medicines – other hypotensives.

Mechanism of action

TESDYN combines two antihypertensive compounds with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine. The combination of these substances has an additive antihypertensive effect.

Telmisartan:

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II 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. 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 monotherapy. Telmisartan monotherapy does not inhibit human plasma renin or block ion channels. In man, 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 is still measurable up to 48 hours.

After administration of the first dose of telmisartan monotherapy, onset of antihypertensive activity occurs 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.

There is an apparent trend to a dose relationship with regard 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 monotherapy reduces both systolic and diastolic blood pressure without affecting pulse rate.

Amlodipine:

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without a change in filtration fraction or proteinuria.

TESDYN (telmisartan and amlodipine fixed dose combination):

Treatment with each combination dose 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 TESDYN (telmisartan and amlodipine fixed dose combination) was similar irrespective of age and gender, and was similar in patients with and without diabetes. TESDYN (telmisartan and amlodipine fixed dose combination) has not been studied in any patient population other than hypertension.

5.2 Pharmacokinetic properties

Pharmacokinetics of the fixed dose combination:

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

Pharmacokinetics of the single components

Absorption

TELMISARTAN

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When the fixed dose combination is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan was approximately 25 % at a dose of 80/10 mg. By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. The reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

AMLODIPINE

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:

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.

AMLODIPINE

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 hypertensive patients.

Biotransformation

TELMISARTAN

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

AMLODIPINE

Amlodipine is extensively (approximately 90 %) metabolised by the liver to inactive metabolites.

Elimination

TELMISARTAN

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours. 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.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly 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 1 500 mL/min).

AMLODIPINE

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.

Pharmacokinetics in special patient groups

Gender

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.

Elderly

The pharmacokinetics of telmisartan do not differ between younger and elderly 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 plasma concentration-time 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 patients

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.

Paediatric population

No pharmacokinetic data are available in the children and adolescents under the age of 18.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch

Crospovidone

FD & C Blue/Brilliant Blue

Iron oxide black

Magnesium stearate

Mannitol

Meglumine (for pH adjustment)

Microcrystalline cellulose

Povidone

Sodium hydroxide (for pH adjustment)

Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from moisture and light.

6.5 Nature and contents of container

TESDYN is packed into blister packs of 30 tablets as aluminium foil (child resistant) and cold form blister foil or aluminium foil and cold form blister foil.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

TESDYN 40/5 mg: A55/7.1.3/0068

TESDYN 40/10 mg: A55/7.1.3/0069

TESDYN 80/5 mg: A55/7.1.3/0070

TESDYN 80/10 mg: A55/7.1.3/0071

9. DATE OF FIRST AUTHORISATION

14 November 2023