SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MIZART PLUS 40/5 (film-coated tablets)

MIZART PLUS 80/5 (film-coated tablets)

MIZART PLUS 40/10 (film-coated tablets)

MIZART PLUS 80/10 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MIZART PLUS 40/5: Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besylate).

Contains sugar: mannitol 176 mg per tablet.

MIZART PLUS 80/5: Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besylate).

Contains sugar: mannitol 352 mg per tablet.

MIZART PLUS 40/10: Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besylate).

Contains sugar: mannitol 176 mg per tablet.

MIZART PLUS 80/10: Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besylate).

Contains sugar: mannitol 352 mg per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

MIZART PLUS 40/5: White to off-white, film-coated, round shaped, biconvex, bevelled edge tablet imprinted with TM6 using black ink on one side of the tablet and blank on the other side.

MIZART PLUS 40/10: White to off-white, film-coated, oval shaped, biconvex, bevelled edge tablet imprinted with TM7 using black ink on one side of the tablet and blank on the other side.

MIZART PLUS 80/5: White to off-white, film-coated, round shaped, biconvex, bevelled edge tablet imprinted with TM8 using black ink on one side of the tablet and blank on the other side.

MIZART PLUS 80/10: White to off-white, film-coated, oval shaped, biconvex, bevelled edge tablet imprinted with TM9 using black ink on one side of the tablet and blank on 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:

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

4.2 Posology and method of administration

Posology:

MIZART PLUS should be taken once daily.

Replacement therapy:

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

Add on therapy:

MIZART PLUS may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone.

The usual starting dose of MIZART PLUS 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. MIZART PLUS should be administered with caution. For telmisartan the dose should not exceed 40/5 mg or 40/10 mg once daily.

Elderly:

No dose adjustment is necessary for elderly patients.

Children and adolescents:

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

Method of administration

Oral use.

MIZART PLUS may be taken with or without food.

4.3 Contraindications

- Known hypersensitivity to telmisartan, amlodipine or to any of the excipients of MIZART PLUS *(see section 6.1)*.
- Hypersensitivity to dihydropyridine derivatives.
- A history of angioedema related to previous therapy with 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 *(see section 4.4)*.
- Porphyria.
- Lithium therapy: Concomitant administration with MIZART PLUS may lead to toxic blood concentrations of lithium *(see section 4.5)*.
- Pregnancy and lactation *(see section 4.6)*.
- The concomitant use of MIZART PLUS with aliskiren-containing medicines is contraindicated *(see section 4.4)*.
- 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

Pregnancy

Should a woman become pregnant while receiving MIZART PLUS, 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 MIZART PLUS and aliskiren is therefore contraindicated (see section 4.3). MIZART PLUS should not be used concomitantly with aliskiren *(see section 4.3)*.

Hepatic impairment:

Telmisartan (ingredient of MIZART PLUS) is mostly eliminated in the bile. 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. MIZART PLUS 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:

When MIZART PLUS 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 MIZART PLUS 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 MIZART PLUS.

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 MIZART PLUS, 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 MIZART PLUS is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy: MIZART PLUS 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 MIZART PLUS 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 MIZART PLUS 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 MIZART PLUS.

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 MIZART PLUS.

Other:

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

Excipient

MIZART PLUS contains mannitol and may have a laxative effect.

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 MIZART PLUS and other medicines.

Concomitant use to be taken into account:

Other antihypertensive medicines:

The blood pressure lowering effect of MIZART PLUS 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 MIZART PLUS: 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 the telmisartan component of MIZART PLUS:

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 MIZART PLUS should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.
A reduced effect of antihypertensive medicines like MIZART PLUS 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 and 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 MIZART PLUS:
Concomitant use requiring caution:
Grapefruit and grapefruit juice:
Administration of MIZART PLUS 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 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

MIZART PLUS should not be used during pregnancy and lactation. Effects related to the mono components are described below.

Pregnancy:

Telmisartan:

Safety in pregnancy and lactation has not been established *(see section 4.3)*. When pregnancy is planned or confirmed, MIZART PLUS should be discontinued. Refer to sections 4.3 and 4.4.

Medicines affecting the renin-angiotensin system, such as MIZART PLUS, 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 MIZART PLUS should be stopped immediately, and, if appropriate, alternative therapy should be started.
Should exposure to MIZART PLUS have occurred from the second trimester of pregnancy, an ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken MIZART PLUS 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

It is not known whether telmisartan (as in MIZART PLUS) 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, MIZART PLUS should not be used by breastfeeding mothers *(see section 4.3)*.

Fertility

No data from controlled clinical studies with the fixed dose combination or with the individual components are available. Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.
In preclinical studies, no effects of telmisartan on male and female fertility were observed.
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.

4.7 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

a) Summary of adverse effects

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

b) Tabulated summary of adverse reactions

The safety and tolerability have been evaluated in five controlled clinical studies with over 3,500 patients, over 2,500 of whom received telmisartan in combination with amlodipine.
Adverse reactions have been ranked under headings of frequency using the following convention: frequent; less frequent and not known (cannot be estimated from the available data).

MedDRA system organ class	**Fixed dose combination of Telmisartan and Amlodipine**	**Telmisartan**	**Amlodipine**
Infections and infestations:			
Less frequent	Cystitis	Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis, sepsis including fatal outcome[1]	
Blood and lymphatic system disorders:			
Less frequent		Anaemia, thrombocytopenia, eosinophilia	Leukocytopenia, thrombocytopenia
Immune system disorders:			
Less frequent		Hypersensitivity, anaphylactic reaction	Hypersensitivity
Metabolism and nutrition disorders:			
Less frequent		Hyperkalaemia, hypoglycaemia (in diabetic patients)	Hyperglycaemia
Psychiatric disorders:			
Less frequent	Depression, anxiety, insomnia		Mood change, confusion
Nervous system disorders:			

MedDRA system organ class	**Fixed dose combination of Telmisartan and Amlodipine**	**Telmisartan**	**Amlodipine**
Frequent	Dizziness		
Less frequent	Somnolence, migraine, headaches, paraesthesia, syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremors		Extrapyramidal syndrome, hypertonia
Eye disorders:			
Frequent			Visual disturbance (including diplopia)
Less frequent		Visual disturbance	Visual impairment
Ear and labyrinth disorders:			
Less frequent	Vertigo		Tinnitus
Cardiac disorders:			
Less frequent	Bradycardia, palpitations	Tachycardia	Myocardial infarction, dysrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders:			

MedDRA system organ class	Fixed dose combination of Telmisartan and Amlodipine	Telmisartan	Amlodipine
Less frequent	Hypotension, orthostatic hypotension, flushing		Vasculitis
Respiratory, thoracic and mediastinal disorders:			
Less frequent	Coughing, interstitial lung disease[3]	Dyspnoea	Dyspnoea, rhinitis
Gastrointestinal disorders:			
Frequent			Altered bowel habits (including diarrhoea and constipation)
Less frequent	Abdominal pain, diarrhoea, nausea, vomiting, gingival hypertrophy, dyspepsia, dry mouth	Flatulence, stomach discomfort	Pancreatitis, gastritis
Hepatobiliary disorders:			
Less frequent		Abnormal hepatic function, liver disorder[2]	
Skin and subcutaneous tissue disorders:			
Less frequent	Pruritus, eczema, erythema, rash	Hyperhidrosis, angioedema (with fatal outcome),	Alopecia, purpura, skin discolouration,

MedDRA system organ class	**Fixed dose combination of Telmisartan and Amlodipine**	**Telmisartan**	**Amlodipine**
		drug eruption, toxic skin eruption, urticaria	Hyperhidrosis, angioedema, Erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity
Frequency unknown			Toxic epidermal Necrolysis
Musculoskeletal and connective tissue disorders:			
Frequent			Ankle swelling
Less frequent	Arthralgia, muscle spasms (Cramps in legs), myalgia, back pain, pain in extremity (leg pain)	Tendon pain (tendinitis like symptoms)	
Renal and urinary disorders:			
Less frequent	Nocturia	Renal impairment including acute renal failure	Micturition disorder, pollakiuria
General disorders and administration site conditions:			
Frequent	Peripheral oedema		

MedDRA system organ class	Fixed dose combination of Telmisartan and Amlodipine	Telmisartan	Amlodipine
Less frequent	Asthenia, chest pain, fatigue, oedema, malaise	Influenza-like illness	Pain
Investigations:			
Less frequent	Increased hepatic enzymes, increased blood uric acid.	Increased blood creatinine, blood creatine phosphokinase increased, Decreased haemoglobin	Increased Weight, decreased weight

1: the event may be a chance finding or related to a mechanism currently not known
2: most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.
3: cases of interstitial lung disease (predominantly interstitial pneumonia and eosinophilic pneumonia) have been reported from post-marketing experience with telmisartan.

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

4.9 Overdose

Symptoms

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

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

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. 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: Medicines acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04. [(2)]

MIZART PLUS combines two antihypertensive medicines with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine. The combination of these medicines 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.

MIZART PLUS:

Treatment with each combination dose of MIZART PLUS 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 MIZART PLUS was similar irrespective of age and gender and was similar in patients with and without diabetes.

MIZART PLUS 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 MIZART PLUS are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from 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.
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

Distribution

Telmisartan is largely bound to plasma protein (> 99,5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vd_{ss}) is approximately 500L. 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 < 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 elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7- 8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity

The small reduction in AUC for telmisartan is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg. Amlodipine exhibits linear pharmacokinetics.

Special Populations:

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Gender

Differences in plasma concentrations of telmisartan were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ in young and elderly patients.
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment

Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have

decreased clearance of amlodipine with resulting increase of approximately 40 - 60 % in AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hypromellose

Magnesium stearate

Mannitol

Meglumine

Povidone (K-30)

Sodium hydroxide

Film coating:

Hypromellose

Titanium dioxide

Imprinting:

Opacode WB Black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ˚C.

Store in the original package to protect from light and moisture.

Remove the tablets from the blister only when required for administration.

6.5 Nature and contents of container

Cold Form Blister Pack: comprises of cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side – OPA/Aluminium/PVC) on one side and hard tempered aluminium foil coated with VMCH heat seal lacquer on the other side. Suitable number of blister strips will be placed in an outer cardboard carton. Pack size: 30’s (blister strips of 10’s).

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBERS

MIZART PLUS 40/5: 51/7.1.3/0743

MIZART PLUS 40/10: 51/7.1.3/0741

MIZART PLUS 80/5: 51/7.1.3/0744

MIZART PLUS 80/10: 51/7.1.3/0742

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the registration certificate: 11 October 2022.

10 DATE OF REVISION OF THE TEXT

27 September 2023.