1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MIZART 40 mg (tablets)

MIZART 80 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

MIZART 40 mg

Each tablet contains 40 mg telmisartan.

Contains sugar: Mannitol 170,200 mg

MIZART 80 mg

Each tablet contains 80 mg telmisartan.

Contains sugar: Mannitol 340,400 mg

3 PHARMACEUTICAL FORM

MIZART 40 mg Tablets: White to off white, oblong, biconvex tablets debossed with “TN 40” on one side and “M” on the other side.

MIZART 80 mg Tablets: White to off white, oblong, biconvex tablets debossed with “TN 80” on one side and “M” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MIZART is indicated in the treatment of mild to moderate hypertension, either alone, or in combination with hydrochlorothiazide.

4.2 Posology and method of administration

Posology

Adults:

The recommended dose is 40 mg once daily.

In cases where the target blood pressure is not achieved, the MIZART dose can be increased to a maximum of 80 mg once daily.

Alternatively, MIZART may be used in combination with a low dose thiazide diuretic such as hydrochlorothiazide 12,5 mg which has been shown to have an additive blood pressure lowering effect with MIZART.

When considering raising the dose, it must be borne in mind that the maximum anti-hypertensive effect is generally attained four to eight weeks after the start of treatment.

Special populations

Elderly population:

No dosing adjustment is necessary.

Renal impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment:

In patients with mild to moderate hepatic impairment the dosage should not exceed 40 mg once daily.

Paediatric population

There are no data on the safety and efficacy of MIZART in children and adolescents up to 18 years.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance telmisartan or to any of the excipients of MIZART.
- 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.
- Porphyria.
- Lithium therapy: Concomitant administration with MIZART may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation *(see section 4.4*).
- Severe hepatic impairment.
- Biliary obstructive disorders.
- The concomitant use of MIZART with aliskiren-containing products is contraindicated (*see section 4.4 and 4.5*).

- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Pregnancy:

Should a woman become pregnant while receiving MIZART, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (*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 is used in patients with mild to moderate impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended (*see section 4.3.*There is no experience regarding the administration of MIZART in patients with a recent kidney transplant.

Intravascular volume depletion:

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of MIZART. Volume and/or sodium depletion should be corrected prior to administration of MIZART.

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 other medicines that affect this system has been associated with acute hypotension, uraemia, oliguria, or acute renal failure (*see section 4.3*).

Primary aldosteronism:

Patients with primary aldosteronism will generally not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system; the use of MIZART is therefore not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

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

Ethnic differences:

Angiotensin converting enzyme inhibitors such as MIZART and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other:

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

Hyperkalaemia:

Hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Adequate monitoring of serum potassium in patients at risk is recommended.

In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years).
- Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma). Close monitoring of serum potassium in at risk patients is recommended (*see section 4.5*).
- Based on experience with the use of other 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 e.g. heparin (*see section 4.5*) may lead to an increase in serum potassium and should therefore not be co-administered with MIZART.

Hepatic impairment:

Telmisartan as contained in MIZART is mostly eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, MIZART should not be given to these patients (*see section 4.3*).

MIZART should be used only with caution in patients with mild to moderate hepatic impairment (*see section 4.3*).

Active gastric or duodenal ulcer or gastro-intestinal pathologies:

Gastro-intestinal bleedings have been reported and this has occurred mainly in patients with baseline gastro-intestinal disease. Caution should be exercised when administering MIZART to this group of patients.

Diabetic patients treated with insulin or antidiabetics:

In these patients hypoglycaemia may occur under MIZART treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) 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 and aliskiren is therefore contraindicated *(see section 4.3).* MIZART should not be used concomitantly with aliskiren *(see section 4.3).*

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers 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 ACE inhibitors/renin-angiotensin receptor blockers.

4.5 Interaction with other medicines and other forms of Interaction

Other antihypertensive medicines:

- MIZART may increase the hypotensive effect of other antihypertensive agents.

- Orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Digoxin:

- For digoxin a 20 % increase in median plasma digoxin trough concentration has been observed (in a single case a 39 %) when given concomitantly with telmisartan.
- Monitoring of plasma digoxin levels should be considered.

Lithium:

Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with telmisartan (*see section 4.3*.

Non-steroidal anti-inflammatory medicinal products:

Concomitant treatment with NSAIDs (including 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 or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

Compounds acting on the Renin-Angiotensin-System, like MIZART, may have synergistic effects. Patients receiving NSAIDs and MIZART should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

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

Corticosteroids (systemic route):

Reduction of the antihypertensive effect.

Other medicinal products acting on the renin-angiotensin-aldosterone system:

As with other medicines acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia *(see section 4.4)*. The risk may increase in case of treatment

combination with other medicines that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium.

Potassium sparing diuretics or potassium supplements:

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium *(see section 4.4*). If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

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 ACE inhibitors, angiotension II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function *(see section 4.3 and 4.4).*

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury *(see section 4.3).*

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Women of childbearing age should ensure effective contraception.

Pregnancy

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

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

Breastfeeding

MIZART is not recommended in breastfeeding and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

MIZART may cause dizziness or drowsiness and have no or negligible effect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	Undesirable effect
	Less frequent
Infections and Infestations:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis, sepsis including fatal outcome
Blood and the lymphatic system disorders:	Anaemia, eosinophilia, thrombocytopenia, neutropenia
Immune system disorders:	Anaphylactic reaction, hypersensitivity, angioedema (also with fatal outcome)
Metabolism and nutrition disorders:	Hyperkalaemia, hypoglycaemia (in diabetic patients)
Psychiatric disorders:	Insomnia, depression, anxiety
Nervous system disorders:	Syncope, somnolence, headache, dizziness, fatigue
Eye disorders:	Visual disturbance
Ear and labyrinth disorders:	Vertigo
Cardiac disorders:	Bradycardia, tachycardia
Vascular disorders:	Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders:	Dyspnoea, cough, interstitial lung disease
Gastrointestinal disorders:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders:	Abnormal hepatic function/liver disorder
Skin and subcutaneous tissue disorders:	Pruritus, hyperhidrosis, rash, eczema, erythema, urticaria, drug eruption, toxic skin eruption, angioedema (also with fatal outcome)
Musculoskeletal, connective tissue and bone disorders:	Back pain (e.g. sciatica), muscle spasms, myalgia, arthralgia, pain in extremity, tendon pain (tendinitis-like symptoms)
Renal and urinary disorders:	Renal impairment including acute renal failure
General disorders and administrative site conditions:	Chest pain, asthenia (weakness), influenza-like illness

Investigations:	Increased blood creatine, decreased haemoglobin, increased blood uric acid, increased hepatic enzyme, increased blood creatinine phosphokinase

Description of selected adverse reactions

Sepsis:

- An increased incidence of sepsis has been reported with telmisartan as contained in MIZART compared with placebo.

Hypotension

Abnormal hepatic function/liver disorder:

- Most cases of abnormal hepatic function/liver disorder occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Interstitial lung disease:

- Cases of interstitial lung disease have been reported in temporal association with the intake of MIZART.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311

4.9 Overdose

Symptoms:

In overdose, side effects can be precipitated and/or be of increased severity *(see section 4.8).*

No data are available with regard to overdose in humans.

The most prominent manifestations of MIZART overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Treatment:

If symptomatic hypotension should occur, supportive treatment should be instituted.

Telmisartan is not removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines – other hypotensives

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. It 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. Telmisartan selectively binds at the AT_1 receptor. The binding is long-lasting. Telmisartan does not inhibit human plasma renin or block ion channels.

In man, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is 50 % at 24 hours and is still measurable up to 48 hours.

After administration of the first dose of MIZART, 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.

The antihypertensive effect persists over 24 hours after dosing.

5.2 Pharmacokinetic properties

Absorption of telmisartan varies. The mean absolute bioavailability for telmisartan is about 50 %.

When telmisartan is taken with food compared to fasting, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). After 3 hours post 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.

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

Telmisartan is highly 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.

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

Telmisartan kinetics is characterised by biexponential decay, 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.

Plasma concentrations were higher in females than in males.

After oral 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) when compared with hepatic blood flow (about 1 500 ml/min).

Elderly patients:

The pharmacokinetics of telmisartan does not differ between younger and elderly patients.

Patients with 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.

Patients with hepatic impairment:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, mannitol, meglumine and povidone (k-30), sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ˚C.

MIZART Tablets should not be removed from their foil pack until required for administration.

Keep the bottles tightly closed.

6.5 Nature and contents of container

Cold form blister pack comprising of cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side i.e. OPA/Al/PVC) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side in a carton. Each carton consists of 3 blister strips (10 tablets/blister).

or

High density polyethylene (HDPE) bottle pack comprising of round wide mouth white HDPE bottle with white opaque polypropylene (PP) screw closure with aluminium induction sealing wad. A desiccant (silica gel) and absorbent cotton is placed in the bottle. Bottle pack is packaged in a carton.

Pack sizes of 30’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

MIZART 40 mg: 45/7.1.3/0606

MIZART 80 mg: 45/7.1.3/0607

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 June 2014

10 DATE OF REVISION OF TEXT

10 November 2022