AUSTRALIAN PRODUCT INFORMATION

MIZART® HCT

(telmisartan and hydrochlorothiazide) tablet

1 NAME OF THE MEDICINE

Telmisartan and Hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MIZART HCT 40/12.5 tablet contains Telmisartan 40 mg and Hydrochlorothiazide 12.5 mg as active ingredients.

Each MIZART HCT 80/12.5 tablet contains Telmisartan 80 mg and Hydrochlorothiazide 12.5 mg as active ingredients.

Each MIZART HCT 80/25 tablet contains Telmisartan 80 mg and Hydrochlorothiazide 25 mg as active ingredients.

Excipients with known effect:

MIZART HCT 40/12.5 tablet: lactose and sulfites

MIZART HCT 80/12.5 and 80/25 tablets: sugars as lactose and sulfites

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablet

40/12.5 mg Tablet:

Each tablet is an oblong shaped, biconvex, bilayered, uncoated tablets with one white to off-white color layer and one pink color mottled layer debossed with ‘L199’. White to off white color layer may contain pink color specks.

80/12.5 mg Tablet:

Each tablet is an oblong shaped, biconvex, bilayered, uncoated tablets with one white to off-white color layer and one pink color mottled layer debossed with ‘L200’. White to off white color layer may contain pink color specks.

80/25 mg Tablet:

Each tablet is an oblong shaped, biconvex, bilayered, uncoated tablets with one white to off-white color layer and one yellow color mottled layer debossed with ‘L201’. White to off white color layer may contain yellow color specks.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MIZART HCT is indicated for the treatment of hypertension. Treatment should not be initiated with these combinations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults: The recommended dose is one tablet once daily.

The dose of telmisartan can be increased before switching to MIZART HCT. Direct change from monotherapy to the fixed combinations may be considered.

MIZART HCT 40/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 40 mg or hydrochlorothiazide.

MIZART HCT 80/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 80 mg or by MIZART HCT 40/12.5 mg.

MIZART HCT 80/25 mg may be administered in patients whose blood pressure is not adequately controlled by MIZART HCT 80/12.5 mg or in patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

Sodium or volume depletion should be corrected before treatment commencement with MIZART HCT.

The maximum antihypertensive effect with MIZART HCT is generally attained 4 to 8 weeks after the start of treatment.

Elderly: No dosing adjustment is necessary. Patients aged 65 years and older should be prescribed MIZART HCT with caution due to increased risk of renal impairment.

Renal impairment: Due to the hydrochlorothiazide component, MIZART HCT must not be used by patients with severe renal dysfunction (creatinine clearance < 30 mL/min, see Section 4.3 CONTRAINDICATIONS). Loop diuretics are preferred to thiazides in this population. Experience in patients with mild to moderate renal impairment has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Hepatic impairment: In patients with mild to moderate hepatic impairment, MIZART HCT should be administered with caution. For telmisartan, the dosage should not exceed 40 mg once daily (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). MIZART HCT is contraindicated in patients with severe hepatic impairment.

Method of Administration:

MIZART HCT tablets are for oral administration.

MIZART HCT may be administered with or without food.

4.3 CONTRAINDICATIONS

- Hypersensitivity to any of the components of the product or sulfonamide-derived substances
- Pregnancy
- Lactation
- Cholestasis and biliary obstructive disorders
- Severe hepatic impairment, coma hepaticum, hepatic precoma
- Severe renal impairment (creatinine clearance < 30 mL/min or serum creatinine > 160 μmol/L), anuria, or acute glomerulonephritis
- Therapy-refractory hyponatraemia

- Hypovolaemia
- Symptomatic hyperuricaemia/gout
- Refractory hypokalaemia, hypercalcaemia
- The concomitant use of MIZART HCT with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2)

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

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 medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor blocker) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function (see Section 4.3 CONTRAINDICATIONS).

Combination use of ACE-inhibitors or angiotensin receptor blockers, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor blocker, an anti-inflammatory drug (NSAID or COX- 2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of MIZART HCT is not recommended.

Diabetes Mellitus

Exploratory post-hoc analyses of two placebo-controlled telmisartan trials suggested an increased risk of fatal myocardial infarction and unexpected cardiovascular death (death occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular cause, and without clinical or post mortem evidence of other etiology) in patients with diabetes mellitus who have no documented medical history of either coronary heart disease or myocardial infarction. In patients with diabetes mellitus, coronary heart disease may be asymptomatic and can therefore remain undiagnosed. Treatment with blood pressure lowering agent telmisartan/hydrochlorothiazide may further reduce coronary perfusion in these patients. For this reason,

patients with diabetes mellitus should undergo specific diagnostics and be treated accordingly before initiating therapy with MIZART HCT.

Aortic and mitral valve stenosis, and obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in telmisartan/hydrochlorothiazide 40/12.5 mg and 80/12.5 mg tablets, minimal or no effects were reported.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

In the clinical trials conducted with telmisartan/hydrochlorothiazide, an increase in uric acid levels and triglyceride levels were observed with increasing dose of hydrochlorothiazide. Consideration should be taken if monitoring of lipids and uric acid levels is needed in patients at risk of metabolic disturbances when titrated to the highest dose of MIZART HCT.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals including when the patient is vomiting excessively or receiving parenteral fluids.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with liver cirrhosis, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the antagonism of the AT_1 receptors by the telmisartan component of telmisartan/hydrochlorothiazide, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with telmisartan/hydrochlorothiazide, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with MIZART HCT (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lactose monohydrate

The maximum recommended daily dose of telmisartan/hydrochlorothiazide contains 84 mg of lactose monohydrate in the dose strength 40/12.5 mg, 180.5 mg in the dose strength 80/12.5 mg, and 169.4 mg of lactose monohydrate in the dose strength 80/25 mg.

Patients with rare hereditary condition of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Mannitol

The maximum recommended daily dose of telmisartan and hydrochlorothiazide combination tablet contains 170 mg mannitol in the dose strength 40/12.5 mg and 340 mg mannitol in the dose strengths 80/12.5 mg and 80/25 mg.

Patients with rare hereditary condition of fructose intolerance should not take this medicine.

Sodium- and/or volume-depleted patients

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, especially volume and/or sodium depletion, should be corrected before the administration of MIZART HCT.

Isolated cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) have been observed with the use of hydrochlorothiazide.

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, MIZART HCT should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Ischaemic heart disease

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

General

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Cases of photosensitivity reactions have been reported with use of thiazide diuretics (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In the event of a photosensitivity reaction occurring during treatment, discontinuation of the treatment is recommended. If resumption of the treatment is essential, areas exposed to the sun or to artificial UVA rays should be protected.

Use in Hepatic Impairment

The majority of telmisartan is eliminated in the bile. Patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. MIZART HCT is, therefore, contraindicated for use in these patients.

MIZART HCT should only be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with telmisartan/hydrochlorothiazide in patients with hepatic impairment.

Use in Renal Impairment and Kidney transplantation

Experience with telmisartan/hydrochlorothiazide is modest in patients with mild to moderate renal impairment and therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. MIZART HCT must not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see Section 4.3 CONTRAINDICATIONS). Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. There is no experience regarding the administration of telmisartan/hydrochlorothiazide in patients with a recent kidney transplant.

Increases in serum creatinine have been observed in studies with ACE inhibitors in patients with single or bilateral renal artery stenosis. An effect similar to that observed with ACE inhibitors should be anticipated with MIZART HCT.

Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Use in the Elderly

See Section 5.2 PHARMACOKINETIC PROPERTIES, Special populations, Elderly Patients.

Paediatric Use

Safety and efficacy of telmisartan/hydrochlorothiazide have not been established in patients aged below 18 years. Use of MIZART HCT is not recommended in children and adolescents.

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Clinical Laboratory Findings.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions linked to telmisartan

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

Compounds which have been studied in pharmacokinetic trials include 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 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16% respectively. The clinical relevance of this observation is not fully known. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamics effects of the combined drugs and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Combining telmisartan with ramipril in the ONTARGET trial resulted in a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope compared to telmisartan alone or ramipril alone (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Telmisartan). Concomitant use of telmisartan and ramipril is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.

Cases have also been reported with angiotensin II receptor blockers, including telmisartan. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with MIZART HCT. Lithium and MIZART HCT should be co-administered with caution. Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with non-steroidal anti-inflammatory drugs (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. Compounds acting on the renin-angiotensin-aldosterone system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.

Telmisartan is not metabolised by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit, or are metabolised by cytochrome P450 enzymes.

Interactions linked to hydrochlorothiazide (HCTZ)

The antihypertensive effect of HCTZ can be potentiated by other diuretics, antihypertensive agents, guanethidine, methyldopa, calcium blockers, ACE inhibitors, ARBs, DRIs, beta-receptor blockers, nitrates, barbiturates, narcotics, phenothiazines, tricyclic antidepressants, vasodilators or by alcohol consumption.

During treatment with HCTZ, there is – at the start of treatment with adjuvant ACE inhibitors (e.g. captopril) – a risk of massive hypotension and worsening renal function. Diuretic treatment should therefore be discontinued 2 – 3 days prior to initiation of therapy with an ACE inhibitor to avoid the possibility of hypotension at the start of therapy.

Salicylates and other non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the antihypertensive and diuretic effect of HCTZ. In patients taking high-dose salicylates, the toxic effect of salicylates on the central nervous system may be potentiated. In patients developing hypovolaemia during treatment with HCTZ, concomitant administration of non-steroidal anti-inflammatory drugs may trigger acute renal failure.

Co-administration of thiazides (including HCTZ) and allopurinol may increase the frequency of hypersensitivity reactions to allopurinol.

Co-administration of thiazides and amantadine may increase the risk of amantadine-related adverse reactions.

There is an increased risk for the onset of hyperglycaemia with concomitant administration of HCTZ and beta-receptor blockers.

The effect of insulin or oral antidiabetics, uric acid-lowering agents, as well as noradrenaline (norepinephrine) and adrenaline (epinephrine), may be attenuated with concomitant use of HCTZ. There is also an increased risk of lactic acidosis when metformin is co-administered with HCTZ. An adjustment of the insulin, oral antidiabetic or uric acid-lowering agent dosage may therefore be required.

In concomitant treatment with cardiac glycosides, myocardial sensitivity to cardiac glycosides will be increased by any hypokalaemia and/or hypomagnesaemia that develops during HCTZ therapy, thereby potentiating the effects and adverse effects of these cardiac glycosides.

Concomitant use of HCTZ and kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, penicillin G, salicylates, amphotericin B, antiarrhythmics or laxatives may lead to increased potassium loss.

In the event of dehydration caused by diuretics, there is an increased risk of acute functional renal failure, particularly during use of high doses of iodinated contrast products. Rehydration before administration of the iodinated product is required.

Concomitant use of natriuretic diuretics and antidepressants, antipsychotics or antiepileptics may lead to increased sodium loss. Caution is advised in the long-term use of these medicinal products.

Concomitant use of thiazide diuretics and cytotoxic agents (e.g. cyclophosphamide, fluorouracil, methotrexate) may lead to a reduction in the renal excretion of cytotoxic agents. Increased bone marrow toxicity (especially granulocytopenia) can be expected.

The bioavailability of thiazide diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), likely due to a decrease in gastrointestinal motility and the gastric emptying rate. In contrast, prokinetic medicinal products such as cisapride may reduce the bioavailability of thiazide diuretics.

Diuretics increase plasma lithium levels. As concomitant administration of HCTZ and lithium leads to potentiation of the cardio-and neurotoxic effects of lithium due to decreased lithium excretion, the lithium level must be monitored in patients receiving HCTZ and lithium. In patients with lithium induced polyuria, diuretics can have a paradoxical antidiuretic effect.

The effect of curare-like muscle relaxants may be potentiated or prolonged by HCTZ. In cases where HCTZ cannot be discontinued before the use of curare-like muscle relaxants, the anaesthetist must be informed of the treatment with HCTZ.

Concomitant use of colestyramine or colestipol reduces the absorption of HCTZ. Single doses of either colestyramine or colestipol resins bind the HCTZ and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. However, the interaction may be minimised by staggered dosing of HCTZ and the resinate, so that HCTZ is taken at least 4 hours before or 4-6 hours after administration of the resinate.

Concomitant use with vitamin D may reduce the excretion of calcium via the urine and potentiate the increase of calcium in serum.

When co-administered with calcium salts, hypercalcaemia may occur due to the increase in tubular calcium reuptake. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Concomitant use with ciclosporin may increase the risk of hyperuricaemia and gout-like complications.

Thiazides can increase the hyperglycaemic effect of diazoxide.

During concomitant use of methyldopa, there have been uncommon reports of haemolysis, caused by the formation of antibodies against HCTZ.

HCTZ may reduce the response to adrenergic amines, such as noradrenaline (norepinephrine). However, the clinical impact of this effect does not justify the exclusion of their use.

The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of telmisartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin B, carbenoxolone, penicillin G sodium, salicylic acid and derivatives). Conversely, based on the experience with the use of other drugs that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. If these drugs are to be prescribed with MIZART HCT, monitoring of potassium plasma levels is advisable.

Periodic monitoring of serum potassium is recommended when MIZART HCT is administered with drugs affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics and drugs known to induce torsades de pointes).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed. The effects on fertility of telmisartan in combination with hydrochlorothiazide have not been evaluated in animal studies.

Telmisartan: The fertility of male and female rats was unaffected at oral telmisartan doses up to 100 mg/kg/day.

Hydrochlorothiazide: No animal fertility studies with hydrochlorothiazide are available for evaluation.

Use in Pregnancy

Pregnancy Category: D

Telmisartan

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

Unless continued angiotensin II receptor blockers therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Although there is no clinical experience with telmisartan/hydrochlorothiazide in pregnant women, *in utero* exposure to drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and even death. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. Therefore, when pregnancy is detected, MIZART HCT should be discontinued as soon as possible.

The use of angiotensin II receptor blockers is contraindicated during the second and third trimesters of pregnancy.

Angiotensin II receptor blockers exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Oligohydramnios reported in this setting, presumably resulting from decreased fetal renal function, has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to occur when drug exposure has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor blocker only during the first trimester should be so informed. Women of child-bearing age should be warned of the potential hazards to their fetus should they become pregnant.

Should exposure to angiotensin II receptor blockers have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II receptor blockers should be closely observed for hypotension, oliguria and hyperkalaemia.

Telmisartan has been shown to cross the placenta in rats. There were no teratogenic effects when telmisartan alone or telmisartan in combination with hydrochlorothiazide were administered orally to rats and rabbits during the period of organogenesis at doses up to 50 mg/kg/day telmisartan and 15.6 mg/kg hydrochlorothiazide. Telmisartan was not teratogenic in rabbits at oral doses up to 45 mg/kg/day, but fetal resorptions were observed at the highest dose level. Administration of 50 mg/kg/day telmisartan to rats during pregnancy and lactation caused a decrease in birth weight and suppression of postnatal growth and development of the offspring. The no-effect dose level in rabbits was 15 mg/kg/day, and corresponded to a plasma AUC value that was about 9 times higher than that anticipated in women at the highest recommended dose. Plasma AUC values of telmisartan and hydrochlorothiazide in rats at the highest dose were both about 5 times that anticipated in women at the highest recommended dose.

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Use in Lactation

MIZART HCT is contraindicated during lactation. It is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk. Thiazides appear in human milk and may inhibit lactation. Lactating women should either not be prescribed MIZART HCT or should discontinue breastfeeding if MIZART HCT is administered.

Telmisartan is excreted in the milk of lactating rats. When administered orally to lactating rats at 50 mg/kg/day, telmisartan suppressed postnatal growth and development of the offspring.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of telmisartan/hydrochlorothiazide on ability to drive and use machines has not been studied. However, when driving or operating machinery it should be taken into account that with antihypertensive therapy, occasionally dizziness, syncope or vertigo may occur. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery. This applies particularly at the start of treatment, when increasing the dose, or switching medications and in interaction with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Telmisartan/hydrochlorothiazide has been evaluated for safety in over 1700 patients, including 716 treated for over six months and 420 for over one year. In clinical trials with telmisartan/hydrochlorothiazide, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with telmisartan and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. Most adverse experiences were mild in intensity and transient in nature and did not require discontinuation of therapy.

The overall incidence and pattern of adverse events reported with telmisartan/hydrochlorothiazide 80/25 mg was comparable with telmisartan/hydrochlorothiazide 80/12.5 mg. A dose-relationship of undesirable effects was not established and they showed no correlation with gender, age or race of the patients.

Adverse events occurring at an incidence of 2% or more in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

TABLE 1 Adverse Events Occurring in ≥ 2% of Telmisartan/Hydrochlorothiazide Patients*

	Telm/HCTZ (n=414) (%)	Placebo (n=74) (%)	Telm (n=209) (%)	HCTZ (n=121) (%)
Body as a whole				
Fatigue	3	1	3	3
Influenza-like symptoms	2	1	2	3
Central/peripheral nervous system				
Dizziness	5	1	4	6
Gastrointestinal system				
Diarrhoea	3	0	5	2
Nausea	2	0	1	2
Respiratory system disorder				
Sinusitis	4	3	3	6
Upper respiratory tract infection	8	7	7	10

*includes all doses of telmisartan (20-160 mg), hydrochlorothiazide (6.25-25 mg), and combinations thereof.

The following adverse events were reported at a rate of 2% or greater in patients treated with telmisartan/hydrochlorothiazide, but were as, or more common in the placebo group: pain, headache, cough, urinary tract infection (including cystitis).

Adverse events occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

The adverse events reported in clinical trials with telmisartan/hydrochlorothiazide (including the dose strengths 40/12.5 mg, 80/12.5 mg and 80/25 mg) are listed below:

Cardiac disorders: arrhythmia, tachycardia

Eye disorders: visual impairment, blurred vision

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: diarrhoea, dry mouth, flatulence, abdominal pain, constipation, dyspepsia, vomiting, gastritis

General disorders and administration site conditions: chest pain, influenza-like illness, pain

Hepatobiliary disorders: abnormal hepatic function / liver disorder*

Infections and infestations: bronchitis, pharyngitis, sinusitis

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

Metabolism and nutrition disorders: hypokalaemia, hyponatraemia, hyperuricaemia

Musculoskeletal, connective tissue and bone disorders: back pain, muscle spasms (cramps in legs), myalgia, arthralgia, pain in extremity (leg pain)

Nervous system disorders: syncope (faint), dizziness, paraesthesia, sleep disorder

Psychiatric disorders: anxiety, depression, insomnia

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonary oedema), dyspnoea

Renal and urinary disorders: renal impairment including acute kidney injury

Skin and subcutaneous tissue disorders: angioedema (including fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria

Vascular disorders: hypotension, orthostatic hypotension

In controlled trials (n=1017), 0.2% of patients treated with telmisartan/hydrochlorothiazide 40/12.5 mg or 80/12.5 mg discontinued due to orthostatic hypotension, and the incidence of dizziness was 4% and 7%, respectively.

Telmisartan

Adverse experiences that have been reported with telmisartan in the indication of hypertension treatment or in patients aged 50 years or older at high risk of developing major cardiovascular events, without regard to causality, are listed below:

Blood and lymphatic system disorders: anaemia, eosinophilia, thrombocytopenia

Cardiac disorders: palpitation, angina pectoris, abnormal ECG, bradycardia, tachycardia

Ear and labyrinth disorders: tinnitus, earache, vertigo

Endocrine disorders: diabetes mellitus

Eye disorders: conjunctivitis, visual impairment

Gastrointestinal disorders: haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders (e.g. abdominal discomfort), diarrhoea, dry mouth, flatulence, abdominal pain, dyspepsia, vomiting

General disorders and administration site conditions: pyrexia, malaise, leg oedema, peripheral oedema, asthenia (weakness), chest pain, influenza-like illness

Hepato-biliary disorders: abnormal hepatic function / liver disorder *

Immune system disorders: allergy, anaphylactic reaction, hypersensitivity

Infections and infestations: sepsis (including fatal outcome), upper respiratory tract infection, urinary tract infection, cystitis, infection, fungal infection, abscess, otitis media

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

Metabolism and nutrition disorders: gout, hypercholesterolaemia, hyperkalaemia, hypoglycaemia (in diabetic patients), hyponatraemia

Musculoskeletal, connective tissue and bone disorders: arthritis, tendon pain (tendonitis like symptoms), back pain, muscle spasms (cramps in legs), myalgia, arthralgia, pain in extremity (leg pain)

Nervous system disorders: somnolence, migraine, hypoaesthesia, syncope (faint)

Psychiatric disorders: nervousness, anxiety, depression, insomnia

Renal and urinary disorders: micturition frequency, renal impairment (including acute kidney injury)

Respiratory, thoracic and mediastinal disorders: asthma, rhinitis, epistaxis, dyspnoea

Skin and subcutaneous tissue disorders: dermatitis, eczema, drug eruption, toxic skin eruption, angioedema (including fatal outcome), erythema, pruritis, rash, hyperhidrosis, urticaria

Vascular disorders: cerebrovascular disorder, flushing, dependent oedema, hypertension, hypotension, orthostatic hypotension

Hydrochlorothiazide

Adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Blood and lymphatic system disorders: anaemia (including aplastic anaemia, haemolytic anaemia), agranulocytosis, myelosuppression, bone marrow failure, leukopenia, thrombocytopenia (sometimes with purpura)

Cardiac disorders: arrhythmia

Eye disorders: xanthopsia, angle-closure glaucoma, choroidal effusion, visual impairment, acute myopia

Gastrointestinal disorders: nausea, pancreatitis, abdominal discomfort, cramping, gastric irritation, diarrhoea, constipation, vomiting

General disorders and administration site conditions: pyrexia, asthenia (weakness)

Hepato-biliary disorders: jaundice, cholestasis

Immune system disorders: hypersensitivity including anaphylactic reactions

Infections and infestations: sialadenitis

Investigations: lipids increased

Metabolism and nutrition disorders: hyperglycaemia, hypovolaemia, hypokalaemia, electrolyte imbalance, hyperlipidaemia, anorexia, decreased appetite, hypomagnesaemia, hypercalcaemia, alkalosis hypochloraemic, diabetes mellitus inadequate control, hyponatraemia, hyperuricaemia

Musculoskeletal, connective tissue and bone disorders: weakness, muscle spasms (cramps in legs)

Nervous system disorders: headache, dizziness, paraesthesia, sleep disorder

Psychiatric disorders: restlessness, depression

Renal and urinary disorders: renal failure, renal dysfunction, interstitial nephritis, renal impairment (including acute kidney injury), glycosuria

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: respiratory distress, pneumonitis, pulmonary oedema, acute respiratory distress syndrome (very rare – see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Skin and subcutaneous tissue disorders: lupus like syndrome, cutaneous lupus erythematosus, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, purpura, photosensitivity reaction, rash, urticaria

Vascular disorders: orthostatic hypotension, vasculitis necrotising

Clinical Laboratory Findings

In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan/hydrochlorothiazide tablets.

Haemoglobin and Haematocrit: Decreases in haemoglobin (≥ 2 g/dL) and haematocrit (≥ 9%) were observed in 1.2% and 0.6% of telmisartan/hydrochlorothiazide patients, respectively, in controlled trials. Changes in haemoglobin and haematocrit were not considered clinically significant and there were no discontinuations due to anaemia.

Creatinine, Blood Urea Nitrogen (BUN): Increases in BUN (≥ 11.2 mg/dL) and serum creatinine (≥ 0.5 mg/dL) were observed in 2.8% and 1.4%, respectively, of patients with hypertension treated with telmisartan/hydrochlorothiazide in controlled trials. No patient discontinued treatment with telmisartan/hydrochlorothiazide due to an increase in BUN or creatinine.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. No telmisartan/hydrochlorothiazide treated patients discontinued therapy due to abnormal hepatic function.

Electrolyte Imbalance: See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Post-Marketing Experience

In addition, the following have also been reported based on post-marketing experience:

Telmisartan and Hydrochlorothiazide

Musculoskeletal and connective tissue disorders: systemic lupus erythematosus

* Most cases of hepatic function / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.

Hydrochlorothiazide

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequency ‘not known’: Non-melanoma skin cancer (Basal cell carcinoma, Squamous cell carcinoma and lip squamous cell carcinoma) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Limited information is available for telmisartan/hydrochlorothiazide with regard to overdose in humans.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.

Therapy

No specific information is available on the treatment of overdose with MIZART HCT. The patient should be closely monitored, and the treatment should be symptomatic and supportive depending on the time since ingestion and the severity of the symptoms. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

Telmisartan is not removed by haemofiltration and is not dialysable. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

MIZART HCT is a combination of an angiotensin II receptor blocker (type AT_1), telmisartan, and a benzothiadiazine (thiazide) diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. MIZART HCT once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan

Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan binds selectively with the AT_1 receptor and does not reveal relevant affinity for other receptors nor does it inhibit human plasma renin or block ion channels. The clinically relevant effect of AT_1 receptor blockade is to lower blood pressure by inhibition of angiotensin II mediated vasoconstriction leading to reduction of systemic vascular resistance. During administration with telmisartan, removal of angiotensin II negative feedback on renin secretion results in increased plasma renin activity, which in turn leads to increases in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppressed aldosterone levels indicate effective angiotensin II receptor blockade. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects or cause oedema.

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

After administration of the first dose of telmisartan/hydrochlorothiazide, onset of antihypertensive activity occurs gradually within 3 hours. The maximal reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly

over 24 hours after dosing and includes the last 4 hours before the next dose. With ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24 hour trough to peak ratio for 40-80 mg doses of telmisartan was >80% for both systolic blood pressure (SBP) and diastolic blood pressure (DBP).

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is independent of gender or age, and has been compared to antihypertensive drugs such as amlodipine, atenolol, enalapril, hydrochlorothiazide, lisinopril and valsartan.

Upon abrupt cessation of treatment, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, transient ischaemic attack, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of patients at high risk of cardiovascular events.

The co-primary objectives of the ONTARGET trial were to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg is superior to ramipril 10 mg alone and if (b) telmisartan 80 mg is not inferior to ramipril 10 mg alone in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. Hypothesis tests were performed using hazard ratios and time-to-event analyses (Kaplan-Meier).

The principal patient exclusion criteria included: symptomatic heart failure or other specific cardiac diseases, syncopal episodes of unknown aetiology or planned cardiac surgery within 3 months of the start of study, uncontrolled hypertension or haemorrhagic stroke.

Patients were randomised to one of the three following treatment groups: telmisartan 80 mg (n=8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n=8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomised patients: 69% of patients had a history of hypertension at randomisation and an additional 14% had actual blood pressure readings ≥ 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. During the study, significantly less telmisartan patients (22.0%) discontinued treatment, compared to ramipril patients (24.4%) and telmisartan/ramipril patients (25.3%). The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Comparison of telmisartan versus ramipril

The choice of the non-inferiority margin of 1.13 was solely based on the results of the HOPE (Heart Outcomes Prevention Evaluation) study. Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for congestive heart failure. The incidence of the primary endpoint was similar in the

telmisartan (16.7%) and ramipril (16.5%) groups. In the intention-to-treat (ITT) analysis, the hazard ratio for telmisartan versus ramipril was 1.01 (97.5% CI 0.93-1.10, p(non-inferiority)=0.0019). The noninferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, p (non-inferiority) =0.0078).

Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125 in both the ITT and PP analyses, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite primary endpoint. The non-inferiority conclusion was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint in subgroups based on age, gender, race, baseline concomitant therapies or underlying diseases.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and nonfatal stroke, the primary endpoint in the reference study HOPE, which had investigated the effect of ramipril versus placebo. The ITT hazard ratio of telmisartan versus ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90-1.08, p(non-inferiority)=0.0004), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, p(non- inferiority)=0.0041).

Comparison of telmisartan plus ramipril combination versus ramipril monotherapy alone

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone, thus superiority of the combination could not be demonstrated. The incidence of the primary endpoint was 16.3% in the telmisartan plus ramipril combination group, compared to the telmisartan (16.7%) and ramipril (16.5%) groups. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination group. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Co-administration with telmisartan tends to reverse the potassium loss associated with these diuretics, presumably through blockade of the renin-angiotensin-aldosterone system. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity. There are no data regarding the effects of telmisartan and telmisartan/hydrochlorothiazide on morbidity and mortality in hypertensive patients.

Clinical Trials

The antihypertensive effects of telmisartan/hydrochlorothiazide were examined in three pivotal 8-week randomised, double-blind clinical trials.

One of the pivotal studies compared telmisartan/hydrochlorothiazide 40/12.5 mg to telmisartan 40 mg, in patients who failed to respond adequately to treatment with telmisartan 40 mg. Following a 4 week run-in period, patients who failed to respond to telmisartan 40 mg monotherapy (DBP > 90 mmHg) were randomised to receive either telmisartan 40 mg (167 patients) or telmisartan/hydrochlorothiazide 40/12.5 mg (160 patients) for 8 weeks. Seated blood pressure was taken 24 hours post-dose at each visit.

Treatment with telmisartan/hydrochlorothiazide 40/12.5 mg lowered DBP by an additional 3.5 mmHg and SBP by 7.4 mmHg compared to telmisartan 40 mg. Both results were highly statistically significant ($p<0.01$). Most of the additional effect was seen at 4 weeks of treatment. Changes in DBP for telmisartan 40 mg

monotherapy were -4.8 mmHg at week 4 and -4.3 mmHg at week 8. Changes in DBP for telmisartan/hydrochlorothiazide 40/12.5 mg were -6.1 mmHg at week 4 and -7.4 mmHg at week 8.

Patients in the telmisartan/hydrochlorothiazide 40/12.5 mg arm had a normalised blood pressure response rate (SBP < 140 mmHg and DBP < 90 mmHg) of 51.6% compared to 23.5% for patients in the telmisartan 40 mg monotherapy arm. The DBP response rate (DBP < 90 mmHg) was 64.8% for the telmisartan/hydrochlorothiazide 40/12.5 mg compared to 40.1% in the monotherapy arm. The SBP response rate (reduction in SBP ≥ 10 mmHg from start of active treatment) was 63.5% for the telmisartan/hydrochlorothiazide 40/12.5 mg compared to 42.6% in the monotherapy arm.

In the other pivotal study, telmisartan/hydrochlorothiazide 80/12.5 mg was compared to telmisartan 80 mg. Patients received telmisartan 40 mg (open label) for 4 weeks. At the end of 4 weeks, patients who failed to respond adequately to telmisartan 40 mg (DBP ≥ 90 mmHg) were titrated to telmisartan 80 mg. At the end of this 4 week period, patients who failed to respond adequately to telmisartan 80 mg (DBP ≥ 90 mmHg) were randomised to receive either telmisartan 80 mg (245 patients) or telmisartan/hydrochlorothiazide 80/12.5 mg (246 patients). Seated blood pressure was recorded 24 hours post-dose at each visit.

Treatment with telmisartan/hydrochlorothiazide 80/12.5 mg lowered DBP by an additional 3.1 mmHg and SBP by 5.7 mmHg compared to telmisartan 80 mg in this group of non-responders to telmisartan 80 mg monotherapy. Both were statistically significant ($p<0.01$). Similar results were seen with standing blood pressure. Most of the additional effect was seen at 4 weeks of treatment. Patients in the telmisartan/hydrochlorothiazide 80/12.5 mg arm had a significantly greater blood pressure response rate (SBP < 140 mmHg and DBP < 90 mmHg) of 41.5% compared to 26.1% for patients in the telmisartan 80 mg arm ($p<0.05$).

In the third pivotal study (n=687 patients evaluated for efficacy), telmisartan/hydrochlorothiazide 80/25 mg was compared to telmisartan/hydrochlorothiazide 80/12.5 mg in patients who failed to respond adequately to treatment with telmisartan/hydrochlorothiazide 80/12.5 mg. Following a 6 week run-in period, patients who failed to respond to telmisartan/hydrochlorothiazide 80/12.5 mg (DBP ≥ 90 mmHg) were randomised to either continue treatment with telmisartan/hydrochlorothiazide 80/12.5 mg (347 patients) or to receive telmisartan/hydrochlorothiazide 80/25 mg (340 patients) for 8 weeks. Seated blood pressure was recorded 24 hours post-dose at each visit.

In this group of non-responders to telmisartan/hydrochlorothiazide 80/12.5 mg, treatment with telmisartan/hydrochlorothiazide 80/25 mg demonstrated an incremental blood pressure lowering effect on DBP by an additional 1.6 mmHg and on SBP by 2.7 mmHg compared to continued treatment with telmisartan/hydrochlorothiazide 80/12.5 mg (difference in adjusted mean changes from baseline, respectively). Both were statistically significant ($p<0.01$). Patients in the telmisartan/hydrochlorothiazide 80/25 mg arm had a significantly greater blood pressure response rate compared to patients in the telmisartan/hydrochlorothiazide 80/12.5 mg arm. The DBP response rate (DBP < 90 mmHg or reduction in DBP ≥ 10 mmHg from baseline) was 59.7% for telmisartan/hydrochlorothiazide 80/25 mg compared to 51.9% for telmisartan/hydrochlorothiazide 80/12.5 mg and the SBP response rate (SBP < 140 mmHg or reduction in SBP ≥ 10 mmHg from baseline) was 65.9% for telmisartan/hydrochlorothiazide 80/25 mg compared to 57.3% for telmisartan/hydrochlorothiazide 80/12.5 mg (both $p<0.05$).

An open-label follow-up study was conducted at the study end of the telmisartan/hydrochlorothiazide 80/25 mg pivotal study, where all patients received telmisartan/hydrochlorothiazide 80/25 mg for 6 months. In this follow-up study, trough seated blood pressure was further decreased by 4.6/3.6 mmHg (SBP/DBP) with telmisartan/hydrochlorothiazide 80/25 mg treatment, resulting in a total reduction of 11.4/9.7 mmHg (SBP/DBP) from baseline of the preceding study. Overall, the DBP response rate (DBP < 90 mmHg or reduction in DBP ≥ 10 mmHg from baseline of the preceding study) was achieved in 74.3% of patients and the SBP response rate (SBP < 140 mmHg or reduction in SBP ≥ 10 mmHg from baseline of the preceding study) was achieved in 77.8% of patients at study end.

In a pooled analysis of two similar 8 week double-blind placebo-controlled clinical trials (n=2121 patients evaluated for efficacy) comparing telmisartan 80 mg/hydrochlorothiazide 25 mg (942 patients) with valsartan 160 mg/hydrochlorothiazide 25 mg (952 patients), a significantly greater blood pressure lowering effect of 2.2/1.2 mmHg (SBP/DBP) was demonstrated (difference in adjusted mean changes from baseline,

respectively) in favour of telmisartan 80 mg/ hydrochlorothiazide 25 mg combination. Both were statistically significant ($p<0.01$).

No statistical differences were found with regard to gender between the different treatment groups in all three pivotal studies. No differences were observed concerning age in the first pivotal study discussed. However, for the second and third pivotal studies, although there were no age differences between treatment groups for DBP response/lowering effect, a trend was observed for a greater SBP response/lowering effect in the elderly. This in part could be due to the fact that the elderly generally respond well to hydrochlorothiazide.

In summary, the data showed that the benefits of telmisartan and hydrochlorothiazide appear to be additive and the blood pressure reduction of telmisartan/hydrochlorothiazide was larger than the blood pressure reduction achieved by either monotherapy component.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population comprised of 71,553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

5.2 PHARMACOKINETIC PROPERTIES

Telmisartan

Absorption

Following oral administration of the fixed dose combination tablets, the t_{max} values for telmisartan vary from 0.5 to 4 hours. Absolute bioavailability of telmisartan was shown to be dose dependent. The mean absolute bioavailability of 40 mg telmisartan was 40%, whereas the mean absolute bioavailability of the 160 mg dose amounted to about 60%.

The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. In a Phase II clinical trial, 40, 80 and 120 mg of telmisartan were administered (in capsules) for 28 days to hypertensive subjects. Maximum plasma concentrations at steady state, $C_{max,ss}$, and AUC_{ss} were determined in 37–39 subjects per dose group.

In this trial, the mean C_{max} showed a more-than-proportional increase with dose, increasing 4.4 fold for a two-fold increase in dose from 40 to 80 mg, and increasing 2.4 fold with a 1.5 fold increase in dose from 80 to 120 mg. The mean AUC_{ss} was nearly proportional with increasing dose, increasing 2.3 fold for a two-fold increase in dose from 40 to 80 mg, and increasing 1.5 fold with a 1.5 fold increase in dose from 80 to 120 mg.

There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose.

When telmisartan is taken with food, 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). The small reduction in AUC should not cause a reduction in the therapeutic efficacy. Therefore, MIZART HCT may be taken with or without food.

Distribution

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 6.6 L/kg.

Metabolism

Telmisartan undergoes substantial first-pass metabolism by conjugation to the acylglucuronide. No pharmacological activity has been shown for the conjugate. Telmisartan is not metabolised by the cytochrome P450 system.

Excretion

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of 18.3-23.0 hours.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (C_{Ltot}) is high (approximately 1000 mL/min) when compared with hepatic blood flow (about 1500 mL/min).

Hydrochlorothiazide

Absorption

Following oral administration of telmisartan/hydrochlorothiazide peak concentrations of hydrochlorothiazide are reached in approximately 1.0–2.5 hours after dosing. The absolute oral bioavailability for hydrochlorothiazide is documented as 50 to 80%.

Distribution

Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83–1.14 L/kg.

Metabolism

Hydrochlorothiazide is not metabolised in man.

Excretion

Hydrochlorothiazide is excreted almost entirely as unchanged drug in urine. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. Renal clearance is about 250-300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 8-10 hours.

Special populations

Elderly patients: The pharmacokinetics of telmisartan do not differ between younger and elderly patients (i.e., patients older than 65 years of age). Patients aged 65 years and older should be prescribed MIZART HCT with caution due to increased risk of renal impairment.

Patients with renal impairment: Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30–60 mL/min, mean about 50 mL/min) no dosage adjustment is necessary in patients with decreased renal function.

Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine clearance of 60 mL/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

Patients with hepatic impairment: Pharmacokinetic studies of telmisartan 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.

Gender: Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no clinically significant increases in blood pressure response or incidences of orthostatic hypotension were found in females. No dosage adjustment is necessary. There was a trend towards

higher plasma concentrations of hydrochlorothiazide in females than in males. This is not considered to be of clinical relevance.

Children: Pharmacokinetic studies of telmisartan have not been investigated in patients less than 18 years of age.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of telmisartan in combination with hydrochlorothiazide has not been evaluated in animal studies.

Telmisartan: Telmisartan was not genotoxic in a battery of tests for gene mutations and clastogenicity.

Hydrochlorothiazide: Hydrochlorothiazide was not genotoxic in a gene mutation assay in bacterial cells, or in tests for clastogenic activity *in vitro* and *in vivo*. However, hydrochlorothiazide had mutagenic activity in a mammalian cell assay (mouse lymphoma cells) and caused an increase in chromosomal aberrations *in vitro* (Chinese hamster lung cells). Hydrochlorothiazide also had a genotoxic activity in the sister chromatid exchange assay in Chinese hamster ovary cells and a nondisjunction assay in *Aspergillus nidulans*.

Carcinogenicity

The carcinogenic potential of telmisartan in combination with hydrochlorothiazide has not been evaluated in animal studies.

Telmisartan: Two-year studies in mice and rats did not show any increases in tumour incidences when telmisartan was administered in the diet at doses up to 1000 and 100 mg/kg/day, respectively. Plasma AUC values at the highest dose levels were approximately 60 and 15 times greater, respectively, than those anticipated in humans at the maximum recommended dose.

Hydrochlorothiazide: Two-year feeding studies in mice and rats showed no evidence of carcinogenic potential in female mice at doses up to approximately 600 mg/kg/day, or in male and female rats at doses up to approximately 100 mg/kg/day. However, there was equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide alone at approximately 600 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: Povidone, lactose monohydrate, magnesium stearate, meglumine, sodium hydroxide, sodium stearylfumarate, purified water and mannitol. MIZART HCT 40/12.5 mg and 80/12.5 mg tablets also contain Pigment Blend PB-24880 Pink (ARTG PI No: 108327) and MIZART HCT 80/25 mg tablets also contain Pigment Blend PB-52290 Yellow (ARTG PI No: 108950) as colouring agent.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light and moisture.

Due to the hygroscopic property of MIZART HCT tablets, they should not be removed from their foil pack until required for administration.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs (Aluminium/Aluminium silver foil) of 28 tablets.

Australian Register of Therapeutic Goods (ARTG)

AUST R 246472 MIZART HCT 40/12.5 mg telmisartan 40 mg and hydrochlorothiazide 12.5 mg tablet blister pack

AUST R 246473 MIZART HCT 80/12.5 mg telmisartan 80 mg and hydrochlorothiazide 12.5 mg tablet blister pack

AUST R 246474 MIZART HCT 80/25 mg telmisartan 80 mg and hydrochlorothiazide 25 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

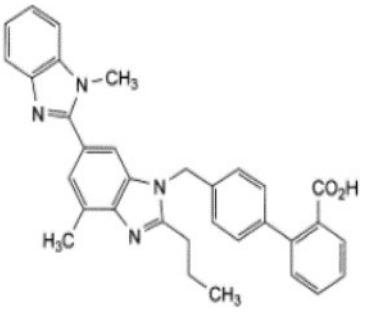
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

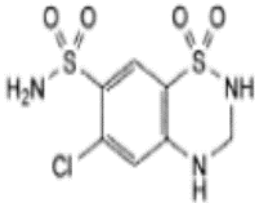
Telmisartan is an off-white to yellowish crystalline powder. It is practically insoluble in water, very slightly soluble in ethanol, slightly soluble in methanol and soluble in a mixture of chloroform and methanol (1:1). Hydrochlorothiazide is a white, or practically white, odourless crystalline powder. It is very slightly soluble in water, and freely soluble in sodium hydroxide solution.

Chemical Structure

Telmisartan



Hydrochlorothiazide



Molecular Formula:

Telmisartan: $C_{33}H_{30}N_4O_2$ Hydrochlorothiazide: $C_7H_8ClN_3O_4S_2$

Molecular Weight:

Telmisartan: 514.6 Hydrochlorothiazide: 297.73

Chemical Name:

Telmisartan: 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'- biphenyl]-2-carboxylic acid (IUPAC nomenclature)

Hydrochlorothiazide: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

CAS Number

Telmisartan: 144701-48-4

Hydrochlorothiazide: 58-93-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

19/08/2016

10 DATE OF REVISION

16/02/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
5.3	Update to Genotoxicity

MIZART® is a Viatris company trade mark

MIZART_HCT_pi\Feb24/00