

AUSTRALIAN PRODUCT INFORMATION – MICARDIS® PLUS telmisartan and hydrochlorothiazide tablets

1 NAME OF THE MEDICINE

telmisartan and hydrochlorothiazide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MICARDIS PLUS is available in three tablet strengths:

- MICARDIS PLUS 40/12.5 mg containing telmisartan 40 mg/hydrochlorothiazide 12.5 mg,
- MICARDIS PLUS 80/12.5 mg containing telmisartan 80 mg/hydrochlorothiazide 12.5 mg, and
- MICARDIS PLUS 80/25 mg containing telmisartan 80 mg/hydrochlorothiazide 25 mg.

Excipients with known effect:

Each 40/12.5 mg tablet and 80/12.5 mg tablet contains 112 mg of lactose monohydrate.

Each 80/25 mg tablet contains 99 mg of lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

MICARDIS PLUS 40/12.5 mg and 80/12.5 mg tablets are red and white oval shaped two layer tablets. Each tablet contains either 40 mg or 80 mg of telmisartan and 12.5 mg of hydrochlorothiazide. The white face of MICARDIS PLUS 40/12.5 mg tablets are marked with H4 and the Boehringer Ingelheim company symbol. The white face of MICARDIS PLUS 80/12.5 mg tablets are marked with H8 and the Boehringer Ingelheim company symbol.

MICARDIS PLUS 80/25 mg tablets are yellow and white oval shaped two layer tablets. Each tablet contains 80 mg of telmisartan and 25 mg of hydrochlorothiazide. The white face of MICARDIS PLUS 80/25 mg tablets are marked with H9 and the Boehringer Ingelheim company symbol.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MICARDIS PLUS 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 MICARDIS PLUS. Direct change from monotherapy to the fixed combinations may be considered.

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

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

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

The maximum antihypertensive effect with MICARDIS PLUS is generally attained 4-8 weeks after the start of treatment.

MICARDIS PLUS may be administered with or without food.

Elderly: No dosing adjustment is necessary.

Renal impairment: Due to the hydrochlorothiazide component, MICARDIS PLUS should 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).

Hepatic impairment: In patients with mild to moderate hepatic impairment, the dosage should not exceed MICARDIS PLUS 40/12.5 mg once daily. MICARDIS PLUS is not indicated in patients with severe hepatic impairment (see Section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

- Hypersensitivity to any of the components of the product or sulphonamide-derived substances
- Pregnancy
- Lactation
- Cholestasis and biliary obstructive disorders
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance < 30 mL/min)
- Refractory hypokalaemia, hypercalcaemia
- The concomitant use of MICARDIS PLUS with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²)

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.

Use in renal impairment and kidney transplantation

Experience with MICARDIS PLUS is modest in patients with mild to moderate renal impairment and therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. MICARDIS PLUS 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 MICARDIS PLUS 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 MICARDIS PLUS.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with 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 antagonist) 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 antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE-inhibitor or angiotensin receptor antagonist, 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 MICARDIS PLUS 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 the blood pressure lowering agent MICARDIS PLUS 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 MICARDIS PLUS.

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 MICARDIS PLUS 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 MICARDIS PLUS, 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 MICARDIS PLUS.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloreaemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, 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 AT₁ receptors by the telmisartan component of MICARDIS PLUS, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with MICARDIS PLUS, 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 MICARDIS PLUS (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

There is no evidence that MICARDIS PLUS would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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.

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. MICARDIS PLUS is, therefore, contraindicated for use in these patients.

MICARDIS PLUS 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 MICARDIS PLUS in patients with hepatic impairment.

Sorbitol

The maximum recommended daily dose of MICARDIS PLUS tablets contains 169 mg sorbitol in the dose strength 40/12.5 mg and approximately 338 mg sorbitol 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.

Lactose monohydrate

The maximum recommended daily dose of MICARDIS PLUS contains 112 mg of lactose monohydrate in the dose strengths 40/12.5 mg and 80/12.5 mg, and 99 mg of lactose monohydrate in the dose strength 80/25 mg.

Patients with rare hereditary condition of galactose intolerance e.g. galactosaemia 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 should be corrected before the administration of MICARDIS PLUS.

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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)).

Other

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.

Use in the elderly

See Section 5.2 Pharmacokinetic Properties, Special populations, Elderly patients.

Paediatric use

Safety and efficacy of MICARDIS PLUS have not been established in children and adolescents up to 18 years.

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

Telmisartan may increase the hypotensive effect of other antihypertensive agents. 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.

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 antagonists, including telmisartan. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with MICARDIS PLUS. Lithium and MICARDIS PLUS should be co-administered with caution. Therefore, serum lithium level monitoring is advisable during concomitant 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 (amphotericin), 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 MICARDIS PLUS, monitoring of potassium plasma levels is advisable.

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 MICARDIS PLUS should be adequately hydrated and be monitored for renal function at the beginning of combined treatment. The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.

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

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.

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

Pharmacodynamics 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.

The following drugs may interact with thiazide diuretics when administered concurrently:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulins): Dosage adjustment of the antidiabetic drug may be required (see Section 4.4 Special warnings and precautions for use).

Metformin: There is a risk of lactic acidosis when co-administered with hydrochlorothiazide.

Colestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Corticosteroids, ACTH: Electrolyte depletion, particularly hypokalaemia, may be increased.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias (see Section 4.4 Special warnings and precautions for use).

Pressor amines (e.g. noradrenaline (norepinephrine)): The effect of pressor amines may be decreased.

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Treatment for gout: Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts: Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Other interactions: The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide monohydrate, methotrexate) and potentiate their myelosuppressive effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies on fertility in humans 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 (Category D)

Telmisartan:

Angiotensin II receptor antagonists should not be initiated during pregnancy. The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. When pregnancy

is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

Although there is no clinical experience with MICARDIS PLUS 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, MICARDIS PLUS should be discontinued as soon as possible.

Preclinical studies with telmisartan do not indicate a teratogenic effect but have shown fetotoxicity.

Angiotensin II receptor antagonist 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 antagonist 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.

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and if appropriate, alternative therapy should be started.

Should exposure to angiotensin II receptor antagonists 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 antagonists 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 fetoplacental 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

MICARDIS PLUS 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 MICARDIS PLUS or should discontinue breastfeeding if MICARDIS PLUS 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 MICARDIS PLUS 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 or drowsiness may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 <https://www.tga.gov.au/reporting-problems>.

MICARDIS PLUS 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 MICARDIS PLUS, 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 MICARDIS PLUS 80/25 mg was comparable with MICARDIS PLUS 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 MICARDIS PLUS (including the dose strengths 40/12.5 mg, 80/12.5 mg and 80/25 mg) are listed below:

Cardiac disorders: cardiac arrhythmias, tachycardia

Eye disorders: abnormal vision, transient 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 symptoms, pain

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

Infections and infestations: bronchitis, pharyngitis, sinusitis

Investigations: increase in creatinine, increase in liver enzymes, increase in blood creatine phosphokinase, increase in uric acid

Metabolism and nutrition disorders: hypokalaemia, hyponatraemia, hyperuricaemia

Musculoskeletal, connective tissue and bone disorders: back pain, muscle spasm, myalgia, arthralgia, leg pain, cramps in legs

Nervous system disorders: syncope / faint, dizziness, paraesthesia, sleep disturbances, insomnia

Psychiatric disorders: anxiety, depression

Reproductive system and breast disorders: impotence

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

Skin and subcutaneous tissue disorders: angioedema (with fatal outcome), erythema, pruritus, rash, sweating increased, urticaria

Vascular disorders: hypotension (including orthostatic hypotension)

In controlled trials (n=1017), 0.2% of patients treated with MICARDIS PLUS 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

Other 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

Ear and labyrinth disorders: tinnitus, earache

Endocrine disorders: diabetes mellitus

Eye disorders: conjunctivitis

Gastrointestinal disorders: haemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders (e.g. stomach upset)

General disorders and administration site conditions: fever, malaise, leg oedema, peripheral oedema, asthenia (weakness)

Immune system disorders: allergy, anaphylactic reaction, hypersensitivity

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

Investigations: decrease in haemoglobin

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

Musculoskeletal, connective tissue and bone disorders: arthrosis, arthritis, tendon pain (tendinitis like symptoms)

Nervous system disorders: somnolence, migraine, hypoaesthesia

Psychiatric disorders: nervousness

Renal and urinary disorders: micturition frequency, renal impairment including acute renal failure (see Section 4.4 Special warnings and precautions for use)

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

Skin and subcutaneous tissue disorders: dermatitis, eczema, drug eruption, toxic skin eruption

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

Hydrochlorothiazide

Other 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, bone marrow depression, neutropenia / leukopenia, thrombocytopenia (sometimes with purpura)

Eye disorders: xanthopsia, acute myopia, acute angle-closure glaucoma

Endocrine disorders: loss of diabetic control

Gastrointestinal disorders: nausea, pancreatitis, stomach upset, cramping, gastric irritation

General disorders and administration site conditions: fever

Hepato-biliary disorders: jaundice (hepatocellular or cholestatic jaundice)

Immune system disorders: anaphylactic reactions, allergy

Infections and infestations: sialadenitis

Investigations: increase in triglycerides

Metabolism and nutrition disorders: hyperglycaemia, cause or exacerbate volume depletion, electrolyte imbalance, hypercholesterolaemia, anorexia, loss of appetite, hypomagnesaemia, hypercalcaemia, hypochloreaemic alkalosis

Musculoskeletal, connective tissue and bone disorders: weakness

Nervous system disorders: headache, light-headedness

Psychiatric disorders: restlessness

Renal and urinary disorders: renal failure, renal dysfunction, interstitial nephritis, glycosuria

Skin and subcutaneous tissue disorders: cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, purpura, photosensitivity reactions, cutaneous vasculitis

Vascular disorders: necrotizing angiitis (vasculitis)

Clinical Laboratory Findings

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

Haemoglobin and Haematocrit: Decreases in haemoglobin (≥ 2 g/dL) and haematocrit ($\geq 9\%$) 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 MICARDIS PLUS in controlled trials. No patient discontinued treatment with MICARDIS PLUS 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:

MICARDIS PLUS

Immune system disorders: exacerbation or activation of 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 and Squamous cell carcinoma) (see Section 4.4 Special Warnings and Precautions for Use and Section 5.1 Pharmacodynamic Properties, Clinical Trials).

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

Limited information is available for MICARDIS PLUS with regard to overdose in humans.

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

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) 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.

No specific information is available on the treatment of overdose with MICARDIS PLUS. 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 haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Angiotensin II Antagonists and Diuretics

ATC code: C09DA07

MICARDIS PLUS is a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. MICARDIS PLUS 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 AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan binds selectively with the AT₁ 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 AT₁ 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 MICARDIS PLUS, 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 \geq 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, $p(\text{non-inferiority})=0.0019$). The non-inferiority result was confirmed in the per-protocol (PP) analysis, where the hazard ratio was 1.02 (97.5% CI 0.93-1.12, $p(\text{non-inferiority})=0.0078$). 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 non-fatal 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, $p(\text{non-inferiority})=0.0004$), and confirmed by the PP hazard ratio of 1.00 (97.5% CI 0.91-1.11, $p(\text{non-inferiority})=0.0041$).

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 MICARDIS PLUS were examined in three pivotal 8-week randomised, double-blind clinical trials.

One of the pivotal studies compared MICARDIS PLUS 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 \geq 90 mmHg) were randomised to receive either telmisartan 40 mg (167 patients) or MICARDIS PLUS 40/12.5 mg (160 patients) for 8 weeks. Seated blood pressure was taken 24 hours post-dose at each visit.

Treatment with MICARDIS PLUS 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 MICARDIS PLUS 40/12.5 mg were -6.1 mmHg at week 4 and -7.4 mmHg at week 8.

Patients in the MICARDIS PLUS 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 MICARDIS PLUS 40/12.5 mg compared to 40.1% in the monotherapy arm. The SBP response rate (reduction in SBP \geq 10 mmHg from start of active treatment) was 63.5% for the MICARDIS PLUS 40/12.5 mg compared to 42.6% in the monotherapy arm.

In the other pivotal study, MICARDIS PLUS 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 \geq 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 \geq 90 mmHg) were randomised to receive either telmisartan 80 mg (245 patients) or MICARDIS PLUS 80/12.5 mg (246 patients). Seated blood pressure was recorded 24 hours post-dose at each visit.

Treatment with MICARDIS PLUS 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 MICARDIS PLUS 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), MICARDIS PLUS 80/25 mg was compared to MICARDIS PLUS 80/12.5 mg in patients who failed to respond adequately to treatment with MICARDIS PLUS 80/12.5 mg. Following a 6 week run-in period, patients who failed to respond to MICARDIS PLUS 80/12.5 mg (DBP \geq 90 mmHg) were randomised to either continue treatment with MICARDIS PLUS 80/12.5 mg (347 patients) or to receive MICARDIS PLUS 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 MICARDIS PLUS 80/12.5 mg, treatment with MICARDIS PLUS 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 MICARDIS PLUS 80/12.5 mg (difference in adjusted mean changes from baseline, respectively). Both were statistically significant ($p < 0.01$). Patients in the MICARDIS PLUS 80/25 mg arm had a significantly greater blood pressure response rate compared to patients in the MICARDIS PLUS 80/12.5 mg arm. The DBP response rate (DBP $<$ 90 mmHg or reduction in DBP \geq 10 mmHg from baseline) was 59.7% for

MICARDIS PLUS 80/25 mg compared to 51.9% for MICARDIS PLUS 80/12.5 mg and the SBP response rate (SBP < 140 mmHg or reduction in SBP \geq 10 mmHg from baseline) was 65.9% for MICARDIS PLUS 80/25 mg compared to 57.3% for MICARDIS PLUS 80/12.5 mg (both $p < 0.05$).

An open-label follow-up study was conducted at the study end of the MICARDIS PLUS 80/25 mg pivotal study, where all patients received MICARDIS PLUS 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 MICARDIS PLUS 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 \geq 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 \geq 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 MICARDIS PLUS 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 ($\geq 50,000$ 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 ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg). (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse effects (Undesirable effects)).

5.2 PHARMACOKINETIC PROPERTIES

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, MICARDIS PLUS may be taken with or without food.

Following oral administration of MICARDIS PLUS 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

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.

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

Hydrochlorothiazide is not metabolised in man.

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 (CL_{tot}) is high (approximately 1000 mL/min) when compared with hepatic blood flow (about 1500 mL/min).

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 does not differ between younger and elderly patients (i.e., patients older than 65 years of age).

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*. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

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

The excipients in each tablet are povidone, lactose monohydrate, maize starch, magnesium stearate, meglumine, microcrystalline cellulose, sodium hydroxide, sodium starch glycollate type A and sorbitol. MICARDIS PLUS 40/12.5 mg and 80/12.5 mg tablets also contain iron oxide red CI77491 and MICARDIS PLUS 80/25 mg tablets also contain iron oxide yellow CI77492, 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 MICARDIS PLUS tablets below 25°C. Protect from light and moisture.

MICARDIS PLUS tablets should not be removed from their foil pack until required for administration.

6.5 NATURE AND CONTENTS OF CONTAINER

MICARDIS PLUS tablets are available in blister packs containing 7* (sample), 14*, 28, 56* and 98* tablets.

* Not currently distributed in Australia

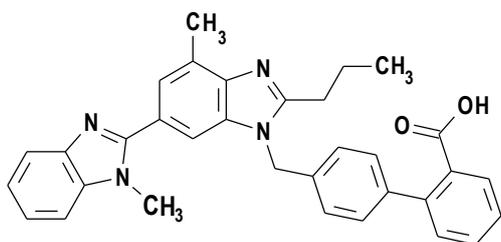
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

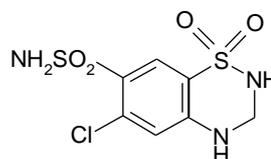
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Telmisartan and hydrochlorothiazide have the following structural formula:



Telmisartan



Hydrochlorothiazide

Telmisartan is a specific angiotensin II receptor (type AT₁) antagonist. The chemical name for telmisartan is 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)-methyl]-[1,1'-biphenyl]-2-carboxylic acid (IUPAC nomenclature). The molecular formula is C₃₃H₃₀N₄O₂ and the molecular weight is 514.6.

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 benzothiadiazine (thiazide) diuretic. The chemical name for hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The molecular formula is $C_7H_8ClN_3O_4S_2$ and the molecular weight is 297.73.

Hydrochlorothiazide is a white, or practically white, odourless crystalline powder. It is very slightly soluble in water, and freely soluble in sodium hydroxide solution.

CAS number

Telmisartan

The CAS number is 144701-48-4.

Hydrochlorothiazide

The CAS number is 58-93-5.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

www.boehringer-ingelheim.com.au

9 DATE OF FIRST APPROVAL

12 September 2002 (40/12.5 and 80/12.5 mg)

22 September 2008 (80/25 mg)

10 DATE OF REVISION

30 April 2019

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|-----------------|---|
| All | Reformatting based on the new Form for PI. |
| 2 | Excipients with known effect “lactose monohydrate” included |
| 4.4 | Update to include safety information in relation to increased risk of Non-melanoma skin cancer (NMSC) with exposure to high cumulative doses of hydrochlorothiazide |
| 4.8 | Update to include new adverse effect of Non-melanoma skin cancer (NMSC) with exposure to high cumulative doses of hydrochlorothiazide Minor editorial change-correction of spelling “photosensitivity” from “photosensivity” |
| 5.1 | Update to include data to Clinical trials section for NMSC. |
| 6.1 | Update to excipient Povidone (K25) to Australian Approved Name Povidone. |
| 8 | Minor editorial change to sponsor address Inclusion of sponsor website |