SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

Macsart 40/80 (Telmisartan Tablets 40mg/80mg)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:

Telmisartan USP..... 40mg/80mg

For Excipients see point 6.1

3. Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Hypertension: Treatment of essential hypertension in adults.

Cardiovascular prevention

Reduction of cardiovascular morbidity in adults with:

• manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or

• type 2 diabetes mellitus with documented target organ damage

4.2 Posology and method of administration

Posology

Treatment of essential hypertension

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily.

Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must

be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Cardiovascular prevention

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.

When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

Telmisartan is contraindicated in patients with severe hepatic impairment.

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

Elderly

No dose adjustment is necessary for elderly patients.

Paediatric population

The safety and efficacy of Telmisartan in children and adolescents aged below 18 years have not been established.

Method of administration

Telmisartan tablets are for once-daily oral administration and should be taken with liquid, with or without food.

Precautions to be taken before handling or administering the medicinal product.

Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity (e.g. anaphylaxis or angioedema) to telmisartan or any other component of this

product. Do not co-administer aliskiren with telmisartan in patients with diabetes.

- Second and third trimesters of pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. 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.

Hypotension

In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

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Impaired Hepatic Function

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and other agents that affect the RAS.

Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min/1.73 m^2).

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

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In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensinaldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

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-angiotensinaldosterone system.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of Telmisartan, 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 Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

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 telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Diabetic patients treated with insulin or antidiabetics

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

Sorbitol

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Telmisartan.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other

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.

4.5 Interaction with other medicinal products and other forms of interaction

Aliskiren: Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min).

Digoxin: When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

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Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3-and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4-and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of Telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, warfarin, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized 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 cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements

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

Concomitant use requiring caution.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use.

Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

4.6 Pregnancy and lactation

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Telmisartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Telmisartan for hypotension, oliguria, and hyperkalemia.

Use in lactation: It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to

discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis

Rare: Sepsis including fatal outcome1

Blood and the lymphatic system disorders

Uncommon: Anaemia

Rare: Eosinophilia, thrombocytopenia

Immune system disorders

Rare: Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders

Uncommon: Hyperkalaemia

Rare: Hypoglycaemia (in diabetic patients)

Psychiatric disorders

Uncommon: Insomnia, depression

Rare: Anxiety

Nervous system disorders

Uncommon: Syncope

Rare: Somnolence

Eye disorders

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Rare: Visual disturbance

Ear and labyrinth disorders

Uncommon: Vertigo

Cardiac disorders

Uncommon: Bradycardia

Rare: Tachycardia

Vascular disorders

Uncommon: Hypotension , orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough

Very rare: Interstitial lung disease

Gastrointestinal disorders

Uncommon: Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting

Rare: Dry mouth, stomach discomfort, dysgeusia

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, hyperhidrosis, rash

Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Muscoloskeletal and connective tissue disorders

Uncommon: Back pain (e.g. sciatica), muscle spasms, myalgia

Rare: Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)

Renal and urinary disorders

Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions

Uncommon: Chest pain, asthenia (weakness)

Rare: Influenza-like illness

Investigations

Uncommon: Blood creatinine increased

Rare: Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

Post marketing Experience

The most frequent spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

4.9 Overdose

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with telmisartan tablets would behypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Mechanism of Action:

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively

blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (> 3,000 fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisa- rtan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are

about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (> 99.5%), mainly albuminand α1 -acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Elimination

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (> 97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Total plasma clearance of telmisartan is > 800 mL/min. Terminal half-life and total clearance appears to be independent of dose.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m²basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan > 100 times and > 25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests

with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m²basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

6. Pharmaceutical Particulars

6.1 List of Excipients

Light Magnesium Oxide, Mannitol, Crospovidone, Colloidal Silicon Dioxide, Sodium Hydroxide, Methanol, Microcrystalline Cellulose, Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30ºC in a dry place. Protect from light.

6.5 Nature and contents of container

Alu/Alu blister pack of 10 Tablets, such 3 Blisters packed in a carton along with pack insert.

Following minimum batch details is coded on foil and carton
Batch No., Mfg. Date and Exp. Date.

6.6 Special Precaution for disposal

None

7. Supplier

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church Road,
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8. WHO Reference Number (Prequalification Programme)

None

9. Date of first Prequalification/ last renewal

None

10. Date of Revision of the Text:

None

References:

1. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3bb7bc69-7752-4c16-9c60-e61eb5355a4d
2. https://www.medicines.org.uk/emc/product/3164/smpc