Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Clotel 40 Tablets
Clotel 80 Tablets

2. Qualitative and quantitative composition

Clotel 40 Tablets
Each film coated tablet contains
Telmisartan BP.....40mg
Chlorthalidone USP.....12.5mg

Clotel 80 Tablets
Each film coated tablet contains
Telmisartan BP.....80mg
Chlorthalidone USP.....12.5mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet.

Both strengths are white circular biconvex shaped film coated tablets, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypertension.

Clotel 40/80 (telmisartan and chlorthalidone fixed dose combination) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

4.2 Posology and method of administration

Posology
This fixed dose combination should be taken in patients whose blood pressure is not adequately controlled by telmisartan alone. Individual dose titration with each of the two components is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

- Clotel 40 may be administered once daily in patients whose blood pressure is not adequately controlled by telmisartan 40mg.
- Clotel 80 may be administered once daily in patients whose blood pressure is not adequately controlled by telmisartan 80mg.

Elderly
No dose adjustment is necessary.
Renal Impairment
Periodic monitoring of renal function is advised (see section 4.4).

Hepatic Impairment
In patients with mild to moderate hepatic impairment the posology should not exceed Clotel 40 mg/12.5 mg once daily. The fixed dose combination is contraindicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function (see section 4.4).

Paediatric Population
The safety and efficacy of the fixed dose combination in children and adolescents aged below 18 have not been established. No data are available.

Method of Administration
The fixed dose combination 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
Clotel tablets 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 (see section 6.6).

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonamide-derived substances.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Patients with anuria.
- Symptomatic hyperuricaemia (history of gout or uric acid calculi
- Severe renal impairment (creatinine clearance < 30 ml/min.)
- Refractory hypokalaemia, hypercalcaemia.
- Concomitant use with aliskerin-containing products in patients with diabetes mellitus or renal impairment (Glomerular Filtration Rate < 60 ml/min/1.73 m2).

4.4 Special warnings and precautions for use

Telmisartan
Telmisartan should be used with caution in patients with hypovolemia, including patients receiving high doses of diuretics. Telmisartan should be used with great care in patients who exhibit signs of hypotension. Intravascular volume and/or salt-depletion increases the risk for

symptomatic hypotension, especially after administration of the first dose. Volume depletion should be corrected prior to the administration of telmisartan.

Heart failure, renal artery stenosis

Telmisartan should be used with caution in patients whose renal function is critically dependent on the activity of the renin-angiotensin-aldosterone system (RAS) (e.g., patients with heart failure). Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists affect the RAS system and have caused increases in serum creatinine in susceptible individuals. Although serum creatinine returns to baseline or stabilizes in most patients with continued use, oliguria, progressive azotemia, and rarely acute renal failure have occurred in this patient population. In addition, ACEIs have been associated with azotemia in patients with unilateral or bilateral renal artery stenosis. Although telmisartan has not been studied in renal artery stenosis, similar effects to the ACEIs might be anticipated due to telmisartan's pharmacology.

Hepatic disease

Telmisartan should be used with caution in patients with hepatic disease. Patients with hepatic impairment, including those with biliary obstruction, have significantly increased plasma telmisartan concentrations compared to patients with normal hepatic function. Thus, in patients with hepatic impairment, begin therapy at a reduced dosage (see Dosage); then adjust dosage to achieve clinical goals.

ACE-inhibitor induced angioedema, angioedema

Anaphylactic reactions (anaphylactoid reactions) and angioedema have been reported with angiotensin II receptor antagonists. Theoretically, angiotensin II receptor antagonists should be less likely than angiotensin converting enzyme inhibitors (ACEIs) to precipitate angioedema because angiotensin II receptor antagonists do not cause accumulation of kinins. However, angioedema (swelling of lips and eyelids, facial rash) has been rarely reported in patients receiving angiotensin II receptor antagonists, including in patients with ACE-inhibitor induced angioedema. While angiotensin II receptor antagonists have been suggested as potential alternatives to ACE inhibitors for patients who experience angioedema due to a lower frequency of associated angioedema , the safety of angiotensin II receptor antagonists in patients with a prior history of ACE-inhibitor induced angioedema has not been definitively established. It is prudent to use substantial caution when prescribing telmisartan in patients with a history of angioedema related to ACE inhibitor therapy. Some authors have recommended that angiotensin II receptor antagonists should be avoided in patients with a history of angioedema, especially in those with ACE-inhibitor induced angioedema.

Hyperkalemia

Telmisartan should be used with caution patients with hyperkalemia. Angiotensin II blockade can theoretically elevate serum potassium concentrations by blocking aldosterone secretion and could worsen preexisting hyperkalemia. Although infrequent, significant hyperkalemia has been reported during post-marketing experience with angiotensin II receptor antagonists. Patients should be instructed not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Black patients

Although telmisartan is effective in reducing blood pressure in Black patients (a low renin population), there is generally a smaller antihypertensive response compared to other ethnic populations. A greater proportion of Black patients will attain blood pressure goals when angiotensin II receptor antagonists are combined with a diuretic.

Pregnancy

Telmisartan can cause fetal harm if administered to a pregnant woman. Once pregnancy is detected, every effort should be made to discontinue telmisartan therapy. Women of child-bearing age should be made aware of the potential risk and telmisartan should only be given after careful counseling and consideration of individual risks and benefits. When used during the second and third trimesters, drugs that affect the renin-angiotensin system (e.g., ACE inhibitors, angiotensin II receptor antagonists) reduce fetal renal function and increase fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Other potential neonatal adverse effects include skull hypoplasia, anuria, and hypotension. Retrospective data indicate that first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. However, a much larger observational study (n = 465,754) found that the risk of birth defects was similar in infants exposed to ACE inhibitors during the first trimester, in infants exposed to other antihypertensives during the first trimester, and in those whose mothers were hypertensive but were not treated. Infants born to mothers with hypertension, either treated or untreated, had a higher risk of birth defects than those born to mothers without hypertension. The authors concluded that the presence of hypertension likely contributed to the development of birth defects rather than the use of medications. In rare cases when another antihypertensive agent cannot be used to treat a pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is observed, discontinue telmisartan unless it is considered life-saving for the mother. It should be noted that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe newborns with histories of in utero exposure to telmisartan for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, blood pressure and renal perfusion support may be required,

as well as exchange transfusion or dialysis to reverse hypotension and/or support decreased renal function.

Breast-feeding

There is no information on the presence of telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats at 1.5 to 2 times those found in plasma from 4 to 8 hours after administration. Due to the potential for serious adverse reactions in the breastfed infant including hypotension, hypokalemia, and renal impairment, breast-feeding is not recommended during telmisartan treatment. Alternative therapies may be considered. Due to low levels in breast milk, guidelines generally consider the ACE inhibitors captopril and enalapril to be compatible with breast-feeding unless high doses are required. In addition, benazepril and quinapril are excreted in low quantities into breast milk and have been suggested as options during breast-feeding. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition.

Children

The safety and effectiveness of telmisartan have not been established in children.

Surgery

In patients undergoing major surgery or during anesthesia with agents that lower blood pressure, telmisartan may enhance hypotensive effects via angiotensin II blockade. Therefore, telmisartan should be used with caution prior to surgery. If hypotension occurs during surgery and/or anesthesia and is considered to be due to blockade of angiotensin II formation, it can be corrected by volume expansion.

Geriatric

During clinical trial evaluation, there were no overall differences in efficacy or safety of telmisartan in geriatric versus younger patients. However, greater sensitivity to the hypotensive effects of telmisartan is possible in geriatric patients due to an age-related decline in renal function. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). According to OBRA, antihypertensive regimens should be individualized to achieve the desired outcome while minimizing adverse effects. Antihypertensives may cause dizziness, postural hypotension, fatigue, and there is an increased risk for falls. Angiotensin receptor blockers (ARBs) may cause angioedema, chronic persistent non-productive cough, and may worsen renal failure. Some agents require a gradual taper to avoid adverse consequences caused by abrupt discontinuation. There are many drug interactions that can potentiate the effects of antihypertensives. Combination therapy of an ARB with a

potassium-sparing diuretic or potassium supplementation has the potential for life-threatening elevations of serum potassium.

Chlorthalidone

Thiazide diuretics (e.g., chlorthalidone) have been associated with a slight increase in serum cholesterol and triglyceride concentrations. Data from long-term studies, however, suggest diuretic-induced cholesterol changes are not clinically significant and do not contribute to coronary heart disease risk.

Sulfonamide hypersensitivity, thiazide diuretic hypersensitivity

Thiazide diuretics are contraindicated in patients with known thiazide diuretic hypersensitivity. According to the manufacturer, chlorthalidone is specifically contraindicated in patients with sulfonamide hypersensitivity. Although thiazide diuretics are sulfonamide derivatives, sulfonamide cross-sensitivity has been rarely documented. Until further data are available, thiazide diuretics should be used with caution in patients with sulfonamide hypersensitivity. Thiazide diuretics do not contain the N4-aromatic amine or the N1-substituent which are present in sulfonamide antibiotics. Non-arylamine sulfonamide derivatives, such as thiazide diuretics, have been proposed to have a lower risk of allergic reactions in patients with sulfonamide allergy, presumably due to lack of an arylamine group at the N4 position (a proposed structural site of action for sulfonamide allergy). One large retrospective cohort study has reported that in patients with the presence of an allergic reaction after exposure to a sulfonamide antibiotic, 9.9% had an allergic reaction after receiving a non-antibiotic sulfonamide derivative, while in patients who lacked an allergic reaction after sulfonamide antibiotic exposure, 1.6% had an allergic reaction after administration of a non-antibiotic sulfonamide derivative (adjusted odds ratio 2.8; 95% CI, 2.1—3.7). A causal relationship between sulfonamide hypersensitivity and allergic reactions with non-arylamine sulfonamide derivatives has not been definitively established and remains controversial. In general, patients with a documented sulfonamide allergy are considered to be predisposed for development of allergic drug reactions.

Electrolyte imbalance, hepatic disease, hypercalcemia, hypochloremia, hypokalemia, hypomagnesemia, hyponatremia, hypotension, metabolic alkalosis

Chlorthalidone-induced fluctuations in serum electrolyte concentration can occur rapidly and precipitate hepatic coma in susceptible patients. Therefore, the drug should be used with caution in patients with hepatic disease. Hyponatremia, hypochloremia, hypomagnesemia, or hypokalemia should be corrected before chlorthalidone is initiated. Initiation of thiazide diuretics under these circumstances can produce life-threatening situations such as cardiac arrhythmias, hypotension, or seizures. Thiazide diuretics may induce metabolic alkalosis

associated with hypokalemia and hypochloremia; this acid/base imbalance is effectively treated with potassium chloride replacement. Chlorthalidone can also cause increase in serum calcium concentrations and should be used with caution in patients with hypercalcemia. Patients receiving diuretics should be monitored for clinical signs of electrolyte imbalance.

Anuria, hypovolemia, renal disease, renal failure, renal impairment
Chlorthalidone should be used cautiously in patients with renal disease such as severe renal impairment or renal failure. Drug-induced hypovolemia can precipitate azotemia in these patients. Therapy should be interrupted or discontinued if renal impairment worsens, as evidenced by an increase in concentrations of BUN, serum creatinine, or nonprotein nitrogen. With the exception of metolazone, thiazide diuretics are considered ineffective when the creatinine clearance is less than 30 ml/minute. Chlorthalidone is contraindicated in patients with anuria.

Orthostatic hypotension, sympathectomy, syncope
Patients with pre-existing hypovolemia or hypotension should have their condition corrected before diuretics such as chlorthalidone are initiated. Orthostatic hypotension may occur during treatment with thiazide diuretics. Orthostatic hypotension can be exacerbated by concurrent use of alcohol, narcotics, or antihypertensive drugs. Excessive hypotension during thiazide diuretic therapy can result in syncope. An increased risk of falls has been reported for older patients receiving thiazide diuretics. In addition, the antihypertensive effects of thiazides may be enhanced in other patients predisposed for orthostatic hypotension, including the post-sympathectomy patient.

Geriatric
Reported clinical experience has not identified differences in responses between geriatric and younger adults. Thiazide and related diuretics may worsen dilutional hyponatremia, especially in geriatric individuals. Greater sensitivity to the usual dosage may also occur in older adult patients, so initial dosages are recommended to be at the lower end of the usual adult dose. An increased risk of falls has been reported for older adult patients receiving thiazide-type diuretics. Patients receiving diuretics should be monitored for clinical signs of acid/base, fluid, or electrolyte imbalances. According to the Beers Criteria, diuretics are considered potentially inappropriate medications (PIMs) in geriatric patients and should be used with caution due to the potential for causing or exacerbating SIADH or hyponatremia; sodium levels should be closely monitored when starting or changing dosages of diuretics in older adults. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities. According to the OBRA guidelines, antihypertensive regimens should be individualized to achieve the desired outcome while minimizing adverse effects. Antihypertensives may cause dizziness, postural

hypotension, fatigue, and there is an increased risk for falls. In addition, diuretics may cause fluid and electrolyte imbalances and may precipitate or exacerbate urinary incontinence. There are many drug interactions that can potentiate the effects of antihypertensives.

Diabetes mellitus, hyperglycemia
Hyperglycemia, reduced glucose tolerance, and glycosuria can occur during chlorthalidone therapy. Blood and/or urine glucose levels should be more carefully assessed in patients with diabetes mellitus who are receiving chlorthalidone. Although hyperglycemia did occur, chlorthalidone has been shown to reduce cardiovascular disease events in elderly diabetic patients with isolated systolic hypertension.

Gout, hyperuricemia
Caution should be used when chlorthalidone is administered to patients with gout or hyperuricemia since thiazide diuretics have been reported to reduce the clearance of uric acid.

Pancreatitis
Thiazide diuretics (e.g., chlorthalidone) have been reported to cause pancreatitis. They should be used with caution in patients with a history of pancreatitis.

Systemic lupus erythematosus (SLE)
Caution should be used when administering thiazides (e.g., chlorthalidone) to patients with a history of systemic lupus erythematosus (SLE) because thiazides have been reported to reactivate or exacerbate this disease.

Sunlight (UV) exposure
Photosensitivity has been reported with thiazide diuretics (e.g., chlorthalidone). Patients should avoid excessive sunlight (UV) exposure and therapy should be discontinued if phototoxicity occurs.

Preeclampsia, pregnancy
Chlorthalidone is structurally related to the thiazide diuretics. Chlorthalidone is classified as FDA pregnancy risk category B. Many experts reserve the use of diuretics for pregnant patients with cardiac disease or essential hypertension, due to the fact that diuretic use may decrease placental perfusion and the data do not indicate a positive benefit of diuretic use on the outcome of preeclampsia during pregnancy. The pregnancy risk factor for thiazide diuretics increases to category D for those pregnant patients with reduced uteroplacental perfusion (e.g., preeclampsia or intrauterine growth retardation (IUGR). In general, the bulk of the evidence does not indicate that thiazide diuretics are teratogenic in the 1st trimester, although, many experts limit their use to the 2nd and 3rd trimesters. Neonatal thrombocytopenia has been reported following maternal use of thiazide

diuretics near term; at term, thiazide diuretics have been reported to cross the placenta. Potential risks from thiazide use include electrolyte imbalances in the newborn, pancreatitis, jaundice, or neonatal complications resulting from such maternal complications such as hyperglycemia, electrolyte imbalance, or hypotension.

Breast-feeding
Thiazide diuretics are excreted in human milk. FDA-approved labeling recommends against breast-feeding during chlorthalidone use. Some thiazide diuretics have been used off-label to suppress lactation, and thus should be used with caution during the establishment of breast-feeding. Previously, the use of bendroflumethiazide, chlorthalidone, chlorothiazide, and hydrochlorothiazide were considered compatible with breast-feeding by the American Academy of Pediatrics, due to lack of noted adverse effects on the nursing infant.

Neonates
Thiazide diuretics (e.g., chlorthalidone) should be avoided in neonates with jaundice. Thiazide-induced hyperbilirubinemia is greater in this patient population.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted with other drugs and Clotel, although studies have been conducted with Telmisartan and Chlorthalidone, separately.
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor antagonists (including telmisartan/HCTZ). Co- administration of lithium and telmisartan/HCTZ is not recommended (see section 4.4). If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Medicinal products associated with potassium loss and hypokalaemia
(e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives)
If these substances are to be prescribed with the Chlorthalidone-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of Chlorthalidone on serum potassium (see section 4.4).

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium,

cyclosporin or other medicinal products such as heparin sodium) If these medicinal products are to be prescribed with the Chlorthalidone-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium and is, therefore, not recommended (see section 4.4).

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when telmisartan/Chlorthalidone is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes.
- class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
-some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine,
cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin,
pentamidine, sparfloxacine, terfenadine, vincamine IV.)

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced arrhythmia (see section 4.4).

Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

Other antihypertensive agents
Telmisartan may increase the hypotensive effect of other antihypertensive agents.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Antidiabetic medicinal products (oral agents and insulin)
Dose adjustment of the antidiabetic medicinal products may be required (see section 4.4).

Non-steroidal anti-inflammatory medicinal products
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dose regimens, COX-2 inhibitors and non- selective NSAIDs) may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics and the antihypertensive effects of angiotensin II receptor antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.
In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Pressor amines (e.g. noradrenaline)
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 chlorthalidone.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol) Dose adjustment of uricosuric medications may be necessary as chlorthalidone may raise the level of serum uric acid. Increase in dose 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 or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dose adjusted accordingly.

Beta-blockers and diazoxide
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Monoamine Oxidase Inhibitors (MAOIs)
Additive hypotensive effects may be seen when MAOIs are combined with antihypertensives.

Tretinoin
As thiazide diuretics are known photosensitizers, concomitant use with tretinoin may augment phototoxicity.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine.
Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

There are no adequate data from the use of telmisartan/HCTZ in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs. 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.
Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). 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 (see sections 4.3 and 4.4).
There is limited experience with thiazides during pregnancy, especially during the first trimester. Animal studies are insufficient. Thiazides cross the placenta. Based on the pharmacological mechanism of action of thiazide drugs, their use during the second and third trimester may compromise foeto- placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Thiazides 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.
Thiazides should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.
Breast-feeding
Because no information is available regarding the use of telmisartan/chlorthalidone during breast-feeding, telmisartan/chlorthalidone is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
Thiazides are excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of telmisartan/chlorthalidone during breast-feeding is not recommended. If telmisartan/chlorthalidone is used during breast-feeding, doses should be kept as low as possible.

Fertility
In preclinical studies, no effects of telmisartan/chlorthalidone on female fertility were observed. Chlorthalidone may cause impotence (erectile dysfunction) in males.

4.7 Effects on ability to drive and use machines.
Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable effects
Telmisartan
Severe
angioedema / Rapid / 0-1.0
anaphylactoid reactions / Rapid / 0-1.0
renal failure (unspecified) / Delayed / 0-1.0
rhabdomyolysis / Delayed / 0-1.0
hyperkalemia / Delayed / Incidence not known
oliguria / Early / Incidence not known
azotemia / Delayed / Incidence not known
teratogenesis / Delayed / Incidence not known

Moderate
skin ulcer / Delayed / 3.0-3.0
orthostatic hypotension / Delayed / 0-1.0
hypotension / Rapid / Incidence not known
eosinophilia / Delayed / Incidence not known
erythema / Early / Incidence not known
hyperuricemia / Delayed / Incidence not known
dyspnea / Early / Incidence not known
gastritis / Delayed / Incidence not known
chest pain (unspecified) / Early / Incidence not known
diabetes mellitus / Delayed / Incidence not known
cystitis / Delayed / Incidence not known
atopic dermatitis / Delayed / Incidence not known
migraine / Early / Incidence not known
angina / Early / Incidence not known
conjunctivitis / Delayed / Incidence not known
palpitations / Early / Incidence not known
hypercholesterolemia / Delayed / Incidence not known
gout / Delayed / Incidence not known
hemorrhoids / Delayed / Incidence not known
hypoglycemia / Early / Incidence not known
depression / Delayed / Incidence not known
edema / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known
anemia / Delayed / Incidence not known
hyponatremia / Delayed / Incidence not known
elevated hepatic enzymes / Delayed / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known

Mild
infection / Delayed / 7.0-7.0
back pain / Delayed / 3.0-3.0
diarrhea / Early / 3.0-3.0
sinusitis / Delayed / 3.0-3.0
cough / Delayed / 1.6-1.6
pharyngitis / Delayed / 1.0-1.0
dizziness / Early / 1.0
rash / Early / 0.3
pruritus / Rapid / 0.3
syncope / Early / Incidence not known
dyspepsia / Early / Incidence not known
gastroesophageal reflux / Delayed / Incidence not known
weakness / Early / Incidence not known
flatulence / Early / Incidence not known
fatigue / Early / Incidence not known
urticaria / Rapid / Incidence not known
insomnia / Early / Incidence not known
tinnitus / Delayed / Incidence not known
muscle cramps / Delayed / Incidence not known

xerostomia / Early / Incidence not known
vertigo / Early / Incidence not known
paresthesias / Delayed / Incidence not known
abdominal pain / Early / Incidence not known
asthenia / Delayed / Incidence not known
vomiting / Early / Incidence not known
anxiety / Delayed / Incidence not known
malaise / Early / Incidence not known
epistaxis / Delayed / Incidence not known
diaphoresis / Early / Incidence not known
fever / Early / Incidence not known
hypoesthesia / Delayed / Incidence not known
arthralgia / Delayed / Incidence not known
myalgia / Early / Incidence not known
rhinitis / Early / Incidence not known
headache / Early / Incidence not known
flushing / Rapid / Incidence not known

Chlorthalidone

Severe

renal failure (unspecified) / Delayed / Incidence not known
azotemia / Delayed / Incidence not known
pancreatitis / Delayed / Incidence not known
agranulocytosis / Delayed / Incidence not known
aplastic anemia / Delayed / Incidence not known
pancytopenia / Delayed / Incidence not known
hemolytic anemia / Delayed / Incidence not known
Stevens-Johnson syndrome / Delayed / Incidence not known
vasculitis / Delayed / Incidence not known
exfoliative dermatitis / Delayed / Incidence not known
toxic epidermal necrolysis / Delayed / Incidence not known

Moderate

hypercalcemia / Delayed / Incidence not known
metabolic alkalosis / Delayed / Incidence not known
hypochloremia / Delayed / Incidence not known
hypokalemia / Delayed / Incidence not known
hypomagnesemia / Delayed / Incidence not known
hyponatremia / Delayed / Incidence not known
hypovolemia / Early / Incidence not known
glycosuria / Early / Incidence not known
hyperglycemia / Delayed / Incidence not known
gout / Delayed / Incidence not known
hyperuricemia / Delayed / Incidence not known
hypercholesterolemia / Delayed / Incidence not known
hypertriglyceridemia / Delayed / Incidence not known
hypotension / Rapid / Incidence not known
orthostatic hypotension / Delayed / Incidence not known
hyperbilirubinemia / Delayed / Incidence not known

jaundice / Delayed / Incidence not known
constipation / Delayed / Incidence not known
xanthopsia / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known
leukopenia / Delayed / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known

Mild
syncope / Early / Incidence not known
vomiting / Early / Incidence not known
diarrhea / Early / Incidence not known
anorexia / Delayed / Incidence not known
nausea / Early / Incidence not known
dizziness / Early / Incidence not known
vertigo / Early / Incidence not known
headache / Early / Incidence not known
paresthesias / Delayed / Incidence not known
polyuria / Early / Incidence not known
libido decrease / Delayed / Incidence not known
muscle cramps / Delayed / Incidence not known
restlessness / Early / Incidence not known
weakness / Early / Incidence not known
rash / Early / Incidence not known
photosensitivity / Delayed / Incidence not known

Description of selected adverse reactions
Hepatic function abnormal/liver disorder
Most cases of hepatic function abnormal/liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Sepsis
In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known (see section 5.1).

Interstitial lung disease
Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Pharmacy and Poisons Board website (https://pv.pharmacyboardkenya.org).

4.9 Overdose

There is limited information available with regard to overdose in humans.

Symptoms: The most prominent manifestations of *Telmisartan* overdose were hypotension and tachycardia; bradycardia, dizziness, increases in serum creatinine and acute renal failure has also been reported. Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

In poisoning due to an overdosage on Chlorthalidone, signs and symptoms that may occur includes: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

There is no specific antidote to chlorthalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken Intravenous fluid and electrolyte replacement may be indicated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Telmisartan

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 telmisartan 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.
In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations, with approximately 40% inhibition persisting for 24 hours.
Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after a single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple-dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, high-density and low-density lipoprotein cholesterol, glucose, or uric acid).
In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Chlorthalidone

Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action. Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the Na^+Cl^- cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.
In persons with normal renal function, diuresis is induced after the administration of 12.5mg chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in edematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.
Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.
In hypertensive individuals, chlorthalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac

output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.
On chronic administration, the antihypertensive effect of chlorthalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.
As with other diuretics, when chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlorthalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.
Combined treatment with other antihypertensives potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.
In renal diabetes insipidus, chlorthalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

5.2 Pharmacokinetic properties

Absorption
Telmisartan

Following oral administration, peak concentrations of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration time curve of about 6% with the 40mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range of 20-160 mg, with greater than proportional increases of plasma concentrations 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 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5-2.0 upon repeated once daily dosing.

Chlorthalidone

The bioavailability of an oral dose of 50mg chlorthalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, C_{max} values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily

doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, are reached after 1 to 2 weeks.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (more than 99.5%), mainly albumin and alpha$_1$-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.

Chlorthalidone
In blood, only a small fraction of chlorthalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlorthalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlorthalidone is about 76% and the major binding protein is albumin.

Chlorthalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlorthalidone daily before and after delivery, chlorthalidone levels in fetal whole blood are about 15% of those found in maternal blood.

Chlorthalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism and Elimination

Telmisartan

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (more than 97%) was eliminated unchanged in the feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

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.

Total plasma clearance of telmisartan is more than 800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Chlorthalidone

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the feces, mainly in unchanged form. Chlorthalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlorthalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special Populations

Pediatric

The pharmacokinetics of telmisartan has not been investigated in patients less than 18 years of age.

Geriatric

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

The elimination of chlorthalidone in elderly patients is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

Gender

Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Impairment

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration. Limited experience is available in patients with severe renal impairment or hemodialysis. A lower starting dose of 20 mg is recommended in these patients.

Renal dysfunction does not alter the pharmacokinetics of chlorthalidone as well, the rate-limiting factor in the elimination of the

drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

Hepatic Impairment

In patients with hepatic impairment, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. 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.

5.3 Preclinical safety data

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (Erythrocytes, Haemoglobin, Haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral sodium chloride solution supplementation. In species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance. No clear evidence of a teratogenic effect was observed, however at toxic dose levels of Telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed. There was no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice. There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics

6. Pharmaceutical particulars

6.1 List of excipients

Sodium hydroxide
Meglumine
Polyvinylpyrrolidone K30
Microcrystalline cellulose pH 102
Sodium stearyl Fumarate
Crospovidone
Magnesium stearate
Tabcoat TC 580097

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage:
Store below 30℃. Protect from direct sunlight. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Alu/Alu blister packs of 3 x10's in unit box with literature insert.

6.6 Special precautions for disposal and other handling:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Dawa Limited,
Plot No 7879/8, Baba Dogo Road –Ruaraka
P.O Box 16630-6200-Nairobi - Kenya.

Manufacturing site address:
Dawa Limited,
Plot No 7879/8, Baba Dogo Road –Ruaraka
P.O Box 16630-6200-Nairobi - Kenya.

8. Marketing authorization number
Clotel 40 - CTD10428
Clotel 80 - CTD10427

9. Date of first registration
03/08/2023

10. Date of revision of the text:
16/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable