# SUMMARY OF PRODUCT CHARACTERISTICS

## Name of the Medical Product

### 1.1 Product Name:

Telmiclar HTZ 40/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 40/12.5 mg)
Telmiclar HTZ 80/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 80/12.5 mg)

### 1.2 Strength:

**Telmiclar HTZ 40/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 40/12.5 mg)**

Each uncoated tablet contains:
Telmisartan USP .....40 mg
Hydrochlorothiazide USP.....12.5 mg

**Telmiclar HTZ 80/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 80/12.5 mg)**

Each uncoated tablet contains:
Telmisartan USP .....80 mg
Hydrochlorothiazide USP .....12.5 mg

### 1.3 Pharmaceutical Dosage Form: Tablets

## 2 Qualitative & Quantitative Composition:

**Telmiclar HTZ 40/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 40/12.5 mg)**

Each uncoated tablet contains:
Telmisartan USP .....40 mg
Hydrochlorothiazide USP .....12.5 mg
Lactose Monohydrate.....134.250 mg
Excipients q.s.
Colour: Red Iron Oxide

**Telmiclar HTZ 80/12.5 (Telmisartan and Hydrochlorothiazide Tablets USP 80/12.5 mg)**

Each uncoated tablet contains:
Telmisartan USP .....80 mg
Hydrochlorothiazide USP .....12.5 mg
Lactose Monohydrate.....268.500 mg
Excipients q.s.

Colour: Red Iron Oxide

*For a full list of excipients, see section 6.1*

**3 Pharmaceutical Dosage Form:**

Bi-layered, oblong shaped, biconvex, uncoated tablets, pinkish brown color with slight mottling in one layer and white to off white color in other layer.

## 4 Clinical Particulars

### 4.1 Therapeutic Indications:

Treatment of essential hypertension.

Telmisartan and Hydrochlorothiazide fixed dose combination is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

### 4.2 Posology and Method of administration:

Telmisartan and Hydrochlorothiazide 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.

• Telmisartan and Hydrochlorothiazide combination 40 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 40 mg

• Telmisartan and Hydrochlorothiazide combination 80 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 80 mg

**Renal impairment**

Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised. Due to the hydrochlorothiazide component, the fixed dose combination is contraindicated in patients with severe renal impairment (creatinine

clearance < 30 mL/min) . Telmisartan is not removed from blood by haemofiltration and is not dialysable.
Periodic monitoring of renal function is advised.

**Hepatic impairment**

In patients with mild to moderate hepatic impairment the posology should not exceed Telmisartan and Hydrochlorothiazide combination 40 mg/12.5 mg once daily. Telmisartan and Hydrochlorothiazide combination is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

**Elderly**

No dose adjustment is necessary.

**Pediatric population**

The safety and efficacy of Telmisartan and Hydrochlorothiazide combination has not been established in patients aged below 18 years. Use of Telmisartan and Hydrochlorothiazide combination is not recommended in children and adolescents

**Method of administration**

Telmisartan and Hydrochlorothiazide combination tablets are for once-daily oral administration and should be swallowed whole with liquid, with or without food.

## 4.3 Contraindications:

- Hypersensitivity to any of the active substances or to any of the excipients.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Second and third trimesters of pregnancy.
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

The concomitant use of Telmisartan and Hydrochlorothiazide combination with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 $m^2$).

## 4.4 Special warning and precautions for use:

**Lactose:** Each tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**Sodium:** Each tablet contains less than 1 mmol Sodium Hydroxide (3.35 mg in Telmiclar HTZ 40/12.5 and 6.70 mg in Telmiclar HTZ 80/12.5) per tablet and Sodium Stearyl Fumarate (3.40 mg in both Telmiclar HTZ 40/12.5 and Telmiclar HTZ 80/12.5), that is to say essentially sodium free

**Mannitol:** This product contain mannitol, May have a mild laxative effect;

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.

Hepatic impairment

Telmisartan and Hydrochlorothiazide combination should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

In addition, Telmisartan and Hydrochlorothiazide combination should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with Telmisartan and Hydrochlorothiazide combination in patients with hepatic impairment.

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.

Renal impairment and kidney transplantation

Telmisartan and Hydrochlorothiazide combination must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). There is no experience regarding the administration of Telmisartan and Hydrochlorothiazide combination in patients with recent kidney transplantation. Experience with Telmisartan and Hydrochlorothiazide combination is modest in the patients with mild to moderate renal impairment, therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Volume and/or sodium 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 Telmisartan and Hydrochlorothiazide combination. Isolated cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy)have been observed with the use of Hydrochlorothiazide.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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

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 and Hydrochlorothiazide combination 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.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance, whereas hypoglycaemia may occur in diabetic patients under insulin or antidiabetic therapy and telmisartan treatment. Therefore, in these patients blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated. Latent diabetes mellitus may become manifest during thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in Telmisartan and Hydrochlorothiazide combination, minimal or no effects were reported.

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

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

- Hypokalaemia

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or Adrenocorticotropic hormone (ACTH).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II ($AT_1$) receptors by the telmisartan component of Telmisartan and Hydrochlorothiazide combination, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan and Hydrochlorothiazide combination, 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 Telmisartan and Hydrochlorothiazide combination.

- Hypochloraemic alkalosis

Chloride deficit is generally mild and usually does not require treatment.

- Hypercalcaemia

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.

- Hypomagnesaemia

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

Ethnic differences

As with all other angiotensin II receptor antagonists, telmisartan is apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

Ischaemic heart disease

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

General

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

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

Cases of photosensitivity reactions have been reported with thiazide diuretics. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal Effusion, Acute Myopia and Angle-Closure Glaucoma

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

National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have beenreported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Telmisartan and Hydrochlorothiazide combination

should be withdrawn and appropriate treatment given.Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Lactose

Each tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sorbitol

Telmisartan and Hydrochlorothiazide combination 40 mg/12.5 mg tablets contain 169 mg sorbitol in each tablet. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product. Each tablet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free.

## 4.5 Interactions with other medicinal products and other forms of Interactions :

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 and Hydrochlorothiazide combination). Co-administration of lithium and Telmisartan and Hydrochlorothiazide combination is not recommended. 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 hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium.

Iodinated contrast products:

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

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine or other medicinal products such as heparin sodium)

If these medicinal products are to be prescribed with the hydrochlorothiazide-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.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when Telmisartan and Hydrochlorothiazide combination 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 antiarrhythmic (e.g. quinidine, hydroquinidine, disopyramide)

- class III antiarrhythmic (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.

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.

Published 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.

Antidiabetic medicinal products (oral agents and insulin)

Dosage adjustment of the antidiabetic medicinal products may be required.

Metformin

Metformin should be used with precaution: risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.

Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage 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 $AUC_{0-24}$ and $C_{max}$ 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.

Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine)

The effect of non-depolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol)

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 or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Beta-blockers and diazoxide

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.

Amantadine

Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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 Pregnancy and Lactation:

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

There are no adequate data from the use of Telmisartan and Hydrochlorothiazide combination in pregnant women. Studies in animals have shown reproductive toxicity.

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 fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). 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.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its 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.

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.

Breast-feeding

Because no information is available regarding the use of Telmisartan and Hydrochlorothiazide combination during breast-feeding, Telmisartan and Hydrochlorothiazide combination is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Telmisartan and Hydrochlorothiazide combination during breast feeding is not recommended. If Telmisartan and Hydrochlorothiazide combination is used during breast feeding, doses should be kept as low as possible.

Fertility

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed. In published preclinical studies, no effects of telmisartan and Hydrochlorothiazide on male and female fertility were observed.

**4.7 Effects on ability to drive and use machine:**

Telmisartan and Hydrochlorothiazide combination can have influence on the ability to drive and use machines. Dizziness or drowsiness may occasionally occur when taking Telmisartan and Hydrochlorothiazide combination. If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

**4.8 Undesirable Effects:**

Summary of the safety profile

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (≥1/10,000 to <1/1,000).

The overall incidence of adverse reactions reported with Telmisartan and Hydrochlorothiazide combination was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients randomised to receive telmisartan plus hydrochlorothiazide (835) or telmisartan alone (636). Dose-relationship of adverse reactions was not established and they showed no correlation with gender, age or race of the patients.

Tabulated list of adverse reactions

Adverse reactions reported in all published clinical trials and occurring more frequently ($p \leq 0.05$) with telmisartan plus hydrochlorothiazide than with placebo are shown below according to system organ class. Adverse reactions known to occur with each component given singly but which have not been

seen in clinical trials may occur during treatment with Telmisartan and Hydrochlorothiazide combination.

Adverse reactions previously reported with one of the individual components may be potential adverse reactions with Telmisartan and Hydrochlorothiazide combination, even if not observed in clinical trials with this product.

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), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies and from post-marketing experience.

| **MedDRA System Organ Class** | **Adverse Reactions** | **Frequency** | | |
|---|---|---|---|---|
| | | **Telmisartan and Hydrochlorothiazide combination** | **Telmisartan[a]** | **Hydrochlorothiazide** |
| **Infections and infestations** | Sepsis including fatal outcome | | rare[2] | |
| | Bronchitis | rare | | |
| | Pharyngitis | rare | | |
| | Sinusitis | rare | | |
| | Upper respiratory tract infection | | uncommon | |
| | Urinary tract infection | | uncommon | |
| | Cystitis | | uncommon | |
| **Neoplasms benign, malignant and unspecified (incl. cysts and polyps)** | Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) | | | not known[2] |
| **Blood and lymphatic** | Anaemia | | uncommon | |
| | Eosinophilia | | rare | |

| | | | | |
|---|---|---|---|---|
| **system disorders** | Thrombocytopenia | | rare | rare |
| | Thrombocytopenic purpura | | | rare |
| | Aplastic anaemia | | | not known |
| | Haemolytic anaemia | | | very rare |
| | Bone marrow failure | | | very rare |
| | Leukopenia | | | very rare |
| | Agranulocytosis | | | very rare |
| **Immune system disorders** | Anaphylactic reaction, | | rare | |
| | Hypersensitivity | | rare | very rare |
| **Metabolism and nutrition disorders** | Hypokalaemia | uncommon | | very common |
| | Hyperuricaemia | rare | | common |
| | Hyponatraemia | rare | rare | common |
| | Hyperkalaemia | | uncommon | |
| | Hypoglycaemia (in diabetic patients) | | rare | |
| | Hypomagnesaemia | | | common |
| | Hypercalcaemia | | | rare |
| | Alkalosis hypochloraemic | | | very rare |
| | Decreased appetite | | | common |
| | Hyperlipidaemia | | | very common |

| | | | | |
|---|---|---|---|---|
| | Hyperglycaemia | | | rare |
| | Diabetes mellitus inadequate control | | | rare |
| **Psychiatric disorders** | Anxiety | uncommon | rare | |
| | Depression | rare | uncommon | rare |
| | Insomnia | rare | uncommon | |
| | Sleep disorders | rare | | rare |
| **Nervous system disorders** | Dizziness | common | | rare |
| | Syncope | uncommon | uncommon | |
| | Paraesthesia | uncommon | | rare |
| | Somnolence | | rare | |
| | Headache | | | rare |
| **Eye disorders** | Visual impairment | rare | rare | rare |
| | Vision blurred | rare | | |
| | Acute angle closure glaucoma | | | not known |
| | Choroidal effusion | | | not known |
| **Ear and labyrinth disorders** | Vertigo | uncommon | uncommon | |
| **Cardiac disorders** | Tachycardia | uncommon | rare | |
| | Arrhythmias | uncommon | | rare |
| | Bradycardia | | uncommon | |
| **Vascular disorders** | Hypotension | uncommon | uncommon | |
| | Orthostatic hypotension | uncommon | uncommon | common |
| | Vasculitis necrotising | | | very rare |
| | Dyspnoea | uncommon | uncommon | |

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|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | Respiratory distress | rare | | very rare |
| | Pneumonitis | rare | | very rare |
| | Pulmonary oedema | rare | | very rare |
| | Cough | | uncommon | |
| | Interstitial lung disease | | very rare[1,2] | |
| | Acute respiratory distress syndrome (ARDS) | | | very rare |
| **Gastrointestinal disorders** | Diarrhoea | uncommon | uncommon | common |
| | Dry mouth | uncommon | rare | |
| | Flatulence | uncommon | uncommon | |
| | Abdominal pain | rare | uncommon | |
| | Constipation | rare | | rare |
| | Dyspepsia | rare | uncommon | |
| | Vomiting | rare | uncommon | common |
| | Gastritis | rare | | |
| | Abdominal discomfort | | rare | rare |
| | Nausea | | | common |
| | Pancreatitis | | | very rare |
| **Hepatobiliary disorders** | Abnormal hepatic function/liver disorder | rare[2] | rare[2] | |
| | Jaundice | | | rare |
| | Cholestasis | | | rare |
| **Skin and subcutaneous tissue disorders** | Angioedema (including fatal outcome) | rare | rare | |
| | Erythema | rare | rare | |
| | Pruritus | rare | uncommon | |

| | | | | |
|---|---|---|---|---|
| | Rash | rare | uncommon | common |
| | Hyperhidrosis | rare | uncommon | |
| | Urticaria | rare | rare | common |
| | Eczema | | rare | |
| | Drug eruption | | rare | |
| | Toxic skin eruption | | rare | |
| | Lupus-like syndrome | | | very rare |
| | Photosensitivity reaction | | | rare |
| | Toxic epidermal necrolysis | | | very rare |
| | Erythema multiforme | | | not known |
| **Muscoloskeletal, connective tissue and bone disorders** | Back pain | uncommon | uncommon | |
| | Muscle spasms (cramps in leg) | uncommon | uncommon | not known |
| | Myalgia | uncommon | uncommon | |
| | Arthralgia | rare | rare | |
| | Pain in extremity (leg pain) | rare | rare | |
| | Tendon pain (tendonitis-like symptoms) | | rare | |
| | Systemic lupus erythematosus | rare[1] | | very rare |
| **Renal and urinary disorders** | Renal impairment | | uncommon | not known |
| | Acute renal failure | | uncommon | uncommon |
| | Glucosuria | | | rare |
| **Reproductive system** | Erectile dysfunction | uncommon | | common |

| | | | | |
|---|---|---|---|---|
| **and breast disorders** | | | | |
| **General disorders and administration site conditions** | Chest pain | uncommon | uncommon | |
| | Influenza-like illness | rare | rare | |
| | Pain | rare | | |
| | Asthenia (weakness) | | uncommon | not known |
| | Pyrexia | | | not known |
| **Investigations** | Blood uric acid increased | uncommon | rare | |
| | Blood creatinine increased | rare | uncommon | |
| | Blood creatine phosphokinase increased | rare | rare | |
| | Hepatic enzyme increased | rare | rare | |
| | Haemoglobin decreased | | rare | |

1 Based on post-marketing experience

2 See subsections below for additional information

a Adverse reactions occurred with similar frequency in placebo and telmisartan treated patients. The overall incidence of adverse reactions reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in placebo controlled trials. The adverse reactions listed above have been accumulated from all clinical trials in patients treated with telmisartan for hypertension or in patients 50 years or older at high risk of cardiovascular events.

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.

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.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

**Reporting of suspected adverse reactions:**

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Authority.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

**4.9 Overdosage:**

There is limited information available for telmisartan with regard to overdose in humans. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, vomiting, increase in serum creatinine, and acute renal failure have also been reported. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, hypochloremia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

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 replacements given quickly.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs) and diuretics

ATC code: C09DA07

Telmisartan and Hydrochlorothiazide combination is a combination of an angiotensin II receptor blocker, 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. Telmisartan and Hydrochlorothiazide combination once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Mechanism of action

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 ($AT_1$) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the $AT_1$ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the $AT_1$ receptor. Telmisartan selectively binds the $AT_1$ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including $AT_2$ and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation

by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. 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.

An 80 mg dose of telmisartan administered to healthy volunteers almost completely inhibits the angiotensin II evoked blood pressure increase. The

inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on 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. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. 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.

Pharmacodynamic effects

Treatment of essential hypertension

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-termtherapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours beforethe next dose as shown by ambulatory blood pressure measurements. This is confirmed by measurements made at thepoint of maximum effect and immediately prior to the next dose (through to peak ratios consistently above 80% afterdoses of 40 mg and 80 mg of telmisartan in placebo controlled clinical studies).

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes ofantihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol,enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over aperiod 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 angiotensinconverting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

**5.2 Pharmacokinetics Properties:**

Concomitant administration of hydrochlorothiazide and telmisartan does not appear to affect the pharmacokinetics of either substance in healthy subjects.

Absorption

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 – 1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42% and 58%, respectively. 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 19% after a 160 mg dose. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of Telmisartan and Hydrochlorothiazide combination peak concentrations of hydrochlorothiazide are reached in approximately 1.0 – 3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60%.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%) mainly albumin and alpha 1- acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Hydrochlorothiazide is 64% protein bound in the plasma and its apparent volume of distribution is 0.8± 0.3 L/kg.

Biotransformation

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans. After a single dose of $^{14}C$-labelled telmisartan the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan: Following either intravenous or oral administration of $^{14}C$-labelled telmisartan most of the administered dose (>97 %) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine. Total plasma clearance of telmisartan after oral administration is >1500 ml/min. Terminal elimination half-life was >20 hours.

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60% of the oral dose is eliminated within 48 hours. Renal clearance is about 250 – 300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

**5.3 Preclinical Safety data:**

In preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

Toxicological findings also well-known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamic (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals.

In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.

No effects of telmisartan on male or female fertility were observed.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the off-springs such as lower body weight and delayed eye opening was observed.

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models.

**6. Pharmaceutical particulars**

**6.1 List of Excipients:**

Sodium Hydroxide, Meglumine, Povidone, Lactose Monohydrate, Crospovidone, Purified Talc, Magnesium Stearate, Lactose, Mannitol, Colloidal Silicon Dioxide, Ferric oxide, Hypromellose, Sodium Stearyl Fumerate and Purified Water.

**6.2 Incompatibilities:** Not applicable

**6.3 Shelf life:** 24 months

**6.4 Special Precautions for storage: Store** below 30°C. Protect from moisture.

**6.5 Nature and contents of container:**

10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert.

**6.6 Special precautions for disposal:** Not applicable.

**7.0 Marketing Authorization Holder:**

Ajanta Pharma Limited,
Ajanta House, Charkop, Kandivli (West),
Mumbai- 400 067, India

**Manufacturing Site Address:**

Ajanta Pharma Limited, Mirza, Palashbari Road, Vill-Kokjhar, Kamrup, Assam. India.

**8.0 Marketing Authorization Numbers:**

CTD11217/22029

**9.0 Date of first registration /renewal of the registration:**

08-12-2025

**10.0 Date of revision of text:**

08-12-2025