

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Telmisartan and Hydrochlorothiazide Alembic 80 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg telmisartan and 12.5 mg hydrochlorothiazide

Excipients with known effect:

Each tablet contains 180.50 mg of lactose monohydrate and 339.88 mg of mannitol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet,

Oblong shaped, biconvex, bilayered with one white to of white color layer and one pink color layer tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Telmisartan and Hydrochlorothiazide Alembic tablets fixed dose combination (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

4.2 Posology and method of administration

Posology

Telmisartan and Hydrochlorothiazide Alembic tablets 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 Alembic 80 mg/12.5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 80mg.
- Telmisartan and Hydrochlorothiazide Alembic 80 mg/12.5 mg tablets may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 80mg.

Special populations:

Patients with 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 Telmisartan and Hydrochlorothiazide Alembic 40 mg/12.5 mg tablets once daily. Telmisartan and Hydrochlorothiazide Alembic tablets are not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function (see section 4.4).

Older people: No dosage adjustment is necessary.

Paediatric population:

The safety and efficacy of Telmisartan and Hydrochlorothiazide Alembic tablets in children and adolescents younger than 18 years of age have not been established. No data are available.

Method of administration

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

Precautions to be taken before handling or administering the medicinal product

Telmisartan and Hydrochlorothiazide Alembic 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.

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients (see section 6.1).
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hepatic impairment: Telmisartan and Hydrochlorothiazide tablets should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency (see section 4.3) 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 tablets 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 tablets 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 tablets should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3). There is no experience regarding the administration of Telmisartan and Hydrochlorothiazide tablets in patients with recent kidney transplantation. Experience with Telmisartan and Hydrochlorothiazide tablets 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.

Intravascular hypovolaemia: 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 tablets.

Dual blockade of the renin-angiotensin-aldosterone system: As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 (see section 4.8).

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 tablets are 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 tablets, 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 hypochloaemic 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 (see section 4.8).

- 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 Adrenocorticotrophic hormone (ACTH) (see section 4.5).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II (AT1) receptors by the telmisartan component of Telmisartan and Hydrochlorothiazide tablets, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan and Hydrochlorothiazide tablets, 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 tablets (see section 4.5).

- Hyponatraemia and hypochloaemic alkalosis

There is no evidence that Telmisartan and Hydrochlorothiazide tablets would reduce or prevent diuretic-induced hyponatraemia. 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 (see section 4.5).

Mannitol and Lactose Monohydrate: This medicinal product contains lactose monohydrate and mannitol. Patients with rare hereditary problems of fructose intolerance and/or with rare hereditary problems of galactose intolerance, the Lapp

lactase deficiency or glucose- galactose malabsorption should not take this medicine.

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.

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

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

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

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). 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 secondary angle-closure glaucoma:
Hydrochlorothiazide, a sulfonamide or sulphonamide derivative drugs can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (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 (see also section 4.8)

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Telmisartan tablets should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.5 Interaction with other medicinal products and other forms of interaction

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

The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) and is not recommended in other patients (see sections 4.3, 4.4).

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 Alembic tablets). Co-administration of lithium and Telmisartan and Hydrochlorothiazide Alembic tablets are 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 hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide 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 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 (see section 4.4).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when Telmisartan and Hydrochlorothiazide Alembic tablets are administered with these 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulphiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloraxacin, terfenadine, vincamine IV.)

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

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

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

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.

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): The effect of nondepolarizing 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 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 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 and Hydrochlorothiazide Alembic tablets 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 fetotoxicity (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 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.

Breastfeeding:

Because no information is available regarding the use of Telmisartan and Hydrochlorothiazide Alembic tablets during breast-feeding, Telmisartan and Hydrochlorothiazide Alembic tablet is not recommended and alternative treatments with better established safety profiles during breast-feeding are

preferable, especially while nursing a newborn 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 Alembic tablets during breast feeding is not recommended. If Telmisartan and Hydrochlorothiazide Alembic tablets is used during breast feeding, doses should be kept as low as possible.

Fertility:

In preclinical studies, no effects of telmisartan and hydrochlorothiazide on male and female fertility were observed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

The overall incidence of adverse events reported with Telmisartan and Hydrochlorothiazide tablets 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 undesirable effects was not established and they showed no correlation with gender, age or race of the patients.

a. Tabulated summary of adverse reactions

Adverse reactions reported in all 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 tablets.

Adverse reactions have been ranked under headings of frequency using the following convention:

very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

| | |
|------------------------------------|--|
| Infections and infestations | |
| Rare: | Bronchitis, pharyngitis, sinusitis |
| Immune system disorders | |
| Rare: | Exacerbation or activation of systemic lupus erythematosus |
| Metabolism and nutrition disorders | |
| Uncommon: | Hypokalaemia |
| Rare: | Hyperuricaemia, hyponatraemia |
| Psychiatric disorders | |
| Uncommon: | Anxiety |
| Rare: | Depression |
| Nervous system disorders | |
| Common: | Dizziness |
| Uncommon: | Syncope, paraesthesia |
| Rare: | Insomnia, sleep disorders, |
| Eye disorders | |
| Rare: | Visual disturbance, vision blurred |
| Ear and labyrinth disorders | |

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|---|--------------------------------------|
| Uncommon: | Vertigo |
| Cardiac disorders | |
| Uncommon: | Tachycardia, arrhythmias |
| Vascular disorders | |
| Uncommon: | Hypotension, orthostatic hypotension |
| Respiratory, thoracic and mediastinal disorders | |
| Uncommon: | Dyspnoea, |

| | |
|---|--|
| Rare: | Respiratory distress (including pneumonitis and pulmonary oedema) |
| Gastrointestinal disorders | |
| Uncommon: | Diarrhoea, dry mouth, flatulence |
| Rare: | Abdominal pain, constipation, dyspepsia, vomiting, gastritis |
| Hepatobiliary disorders | |
| Rare: | Abnormal hepatic function/liver disorder |
| Skin and subcutaneous tissue disorders | |
| Rare: | Angioedema (also with fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria |
| Musculoskeletal, connective tissue and bone disorders | |
| Uncommon: | Back pain, muscle spasms, myalgia |
| Rare: | Arthralgia, muscle cramps, pain in limb |
| Reproductive system and breast disorders | |
| Uncommon: | Erectile dysfunction |
| General disorders and administration site conditions | |
| Uncommon: | Chest pain |
| Rare: | Influenza-like illness, pain |
| Investigations | |
| Uncommon: | Blood uric acid increased |
| Rare: | Blood creatinine increased, blood creatine phosphokinase increased, hepatic enzyme increased |

Additional information on individual components

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

Telmisartan:

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 following adverse drug reactions listed below 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.

| | |
|---|---|
| Infections and infestations | |
| Uncommon: | Upper respiratory tract infection, urinary tract infection including cystitis |
| Rare: | Sepsis including fatal outcome |
| Blood and lymphatic system disorders | |
| Uncommon: | Anaemia |
| Rare: | Eosinophilia, thrombocytopenia |
| Immune system disorders | |
| Rare: | Hypersensitivity, anaphylactic reactions |
| Metabolism and nutrition disorders | |
| Unknown: | Hyperkalaemia |
| Rare: | Hypoglycaemia (in diabetic patients) |
| Cardiac disorders | |
| Uncommon: | Bradycardia |
| Nervous system disorders | |
| Rare: | Somnolence |
| Respiratory, thoracic and mediastinal disorders | |

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|---|--|
| Uncommon: | Cough |
| Very rare: | Interstitial lung disease |
| Gastrointestinal disorders | |
| Rare: | Stomach discomfort |
| Skin and subcutaneous tissue disorders | |
| Rare: | Eczema, drug eruption, toxic skin eruption |
| Musculoskeletal, connective tissue and bone disorders | |
| Rare: | Arthrosis, tendon pain |
| Renal and urinary disorders | |
| Uncommon: | Renal impairment (including acute renal failure) |
| General disorders and administration site conditions | |
| Uncommon: | Asthenia |
| Investigations | |
| Rare: | Haemoglobin decreased |

Hydrochlorothiazide:

Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance (see section 4.4).

Adverse reactions of unknown frequency reported with the use of hydrochlorothiazide alone include:

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|--------------------------------------|---|
| Infections and infestations | |
| Not known: | Sialadenitis |
| Blood and lymphatic system disorders | |
| Not known: | Aplastic Anaemia, haemolytic anaemia, bone marrow failure, leukopenia, neutropenia, agranulocytosis, thrombocytopenia |
| Immune system disorders | |
| Not known: | Anaphylactic reactions, hypersensitivity |
| Endocrine disorders | |

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|---|--|
| Not known: | Diabetes mellitus inadequate control |
| Metabolism and nutrition disorders | |
| Not known: | Anorexia, appetite decreased, electrolyte imbalance, hypercholesterolaemia, hyperglycaemia, hypovolaemia |
| Psychiatric disorders | |
| Not known: | Restlessness |
| Nervous system disorders | |
| Not known: | Light-headedness |
| Eye disorders | |
| Not known | Xanthopsia, acute angle-closure glaucoma, <u>choroidal effusion</u> |
| Vascular disorders | |
| Not known: | Vasculitis necrotizing |
| Gastrointestinal disorders | |
| Not known: | Pancreatitis, stomach discomfort |
| Hepatobiliary disorders | |
| Not known: | Jaundice hepatocellular, jaundice cholestatic |
| Skin and subcutaneous tissue disorders | |
| Not known: | Lupus-like syndrome, photosensitivity reactions, skin vasculitis, toxic epidermal necrolysis |
| Musculoskeletal, connective tissue and bone disorders | |
| Not known: | Weakness |
| Renal and urinary disorders | |
| Not known: | Nephritis interstitial, renal dysfunction, glycosuria |
| General disorders and administration site conditions | |
| Not known: | Pyrexia |
| Investigations | |
| Not known: | Triglycerides increased |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | |

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| Not known: | Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) |
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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.”

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

Intestinal angioedema

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 (hypokalaemia, hypochloraemia) 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 antagonists and diuretics, ATC code: C09DA07

Telmisartan and Hydrochlorothiazide tablets are a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Telmisartan and Hydrochlorothiazide tablets once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT₁) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan selectively binds the AT₁ receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT₂

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.

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-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by measurements made at the point of maximum effect and immediately prior to the next dose (through to peak ratios consistently above 80 % after doses of 40 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 of antihypertensive 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 a period of several days without evidence of rebound hypertension.

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

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

The effects of telmisartan on mortality and cardiovascular morbidity are currently unknown.

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.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effects of Fixed Dose Combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4).

5.2 Pharmacokinetic 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. The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated

administration.

Hydrochlorothiazide: Following oral administration of Telmisartan and Hydrochlorothiazide Alembic tablets 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 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 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 ¹⁴C-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 ¹⁴C-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.

Special populations

Older people: Pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

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. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Renal impairment: Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate

renal impairment (creatinine clearance of 30 – 60 ml/min, mean about 50 ml/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

Hepatic impairment: Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

5.3 Preclinical safety data

In preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, in 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 haemodynamics (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 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.

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

For the foetotoxic potential of the telmisartan/hydrochlorothiazide combination see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium hydroxide

Meglumine

Povidone (K25)

Sodium Stearyl Fumerate

Lactose monohydrate

Magnesium stearate

Colour: Pigment blend PB-24880 pink

Composition of colorants: Lactose Monohydrate, Iron Oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blisters (cold form blister and unprinted aluminum foil).

Pack sizes: Blister with 10 or 28 tablets.

6.6 Special precautions for disposal

Not Applicable.

7 MARKETING AUTHORISATION HOLDER

Strandhaven Ltd t/a Somex Pharma

Ilford, Essex

IG3 8BS .UK

8 MARKETING AUTHORISATION NUMBER(S)

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29/04/2025

10 DATE OF REVISION OF THE TEXT

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