For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TELDAY H
(Telmisartan and Hydrochlorothiazide Tablets U.S.P.)

COMPOSITION
Each uncoated bilayered tablet contains:
Telmisartan I.P. 40 mg
Hydrochlorothiazide I.P. 12.5 mg
Colour: Red oxide of Iron

DOSAGE FORM
Tablet

INDICATION
Fixed dose combination of Telmisartan and Hydrochlorothiazide is indicated for the treatment of hypertension.

DOSE AND METHOD OF ADMINISTRATION
Posology
Telmisartan+hydrochlorothiazide 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+hydrochlorothiazide 40 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 40 mg
• Telmisartan+hydrochlorothiazide 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
Periodic monitoring of renal function is advised.

Hepatic impairment
In patients with mild to moderate hepatic impairment the posology should not exceed Telmisartan+hydrochlorothiazide 40 mg/12.5 mg once daily. Telmisartan+hydrochlorothiazide 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.

Paediatric population
The safety and efficacy of Telmisartan+hydrochlorothiazide in children and adolescents aged below 18 have not been established. No data are available.

Method of administration
Telmisartan+hydrochlorothiazide 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+hydrochlorothiazide 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.

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 with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

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.

Hepatic impairment

Telmisartan and hydrochlorothiazide 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 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 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 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 in patients with recent kidney transplantation. Experience with Telmisartan and Hydrochlorothiazide 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.

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 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, 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, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan and Hydrochlorothiazide H, 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.

- Hyponatraemia and hypochloraemic alkalosis
There is no evidence that Telmisartan and Hydrochlorothiazide 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.

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. 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.

Acute Myopia and Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

DRUG INTERACTION
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). Co-administration of lithium and Telmisartan and Hydrochlorothiazide 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.

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.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when Telmisartan and Hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes.

- class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)

- class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV.)

Digitalis glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced arrhythmia.

Digoxin

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

Other antihypertensive agents

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

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.

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 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.

FERTILITY, 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 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 during breast-feeding, telmisartan and hydrochlorothiazide 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 during breast feeding is not recommended. If Telmisartan and Hydrochlorothiazide 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Telmisartan and Hydrochlorothiazide can have influence on the ability to drive and use machines. Dizziness or drowsiness may occasionally occur when taking Telmisartan and Hydrochlorothiazide.

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 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 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.

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.

Infections and infestations	
Rare:	Bronchitis, pharyngitis, sinusitis
Immune system disorders	Exacerbation or activation of systemic lupus erythematosus[1]
Rare:	
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	
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[2]
Skin and subcutaneous tissue disorders	
Rare:	Angioedema (also with fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria
Muscoloskeletal, 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

1: Based on post-marketing experience

2: For further description, please see sub-section “Description of selected adverse reactions”

Additional information on individual components

Adverse reactions previously reported with one of the individual components may be potential adverse reactions with Telmisartan and Hydrochlorothiazide, 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 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
Rare:	including cystitis

	Sepsis including fatal outcome[3]
Blood and lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic reactions
Metabolism and nutrition disorders	
Uncommon:	Hyperkalaemia
Rare:	Hypoglycaemia (in diabetic patients)
Cardiac disorders	
Uncommon:	Bradycardia
Nervous system disorders	
Rare:	Somnolence
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough
Very rare:	Interstitial lung disease[3]
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

3: For further description, please see sub-section “Description of selected adverse reactions”

Hydrochlorothiazide:

Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance.
Adverse reactions of unknown frequency reported with the use of hydrochlorothiazide alone include:

Infections and infestations	
Not known:	Sialadenitis
Blood and lymphatic system disorders	
Rare:	Thrombocytopenia (sometimes with purpura)

Not known:	Aplastic anaemia, haemolytic anaemia, bone marrow failure, leukopenia, neutropenia, agranulocytosis,
Immune system disorders	
Not known:	Anaphylactic reactions, hypersensitivity
Endocrine disorders	
Not known:	Diabetes mellitus inadequate control
Metabolism and nutrition disorders	
Common:	Hypomagnesaemia
Rare:	Hypercalcaemia
Very rare:	Hypochloraemic alkalosis
Not known:	Anorexia, appetite decreased, electrolyte imbalance, hypercholesterolaemia, hyperglycaemia, hypovolaemia
Psychiatric disorders	
Not known:	Restlessness
Nervous system disorders	
Rare:	Headache
Not known:	Light-headedness
Eye disorders	
Not known	Xanthopsia, acute myopia, acute angle-closure glaucoma
Vascular disorders	
Not known:	Vasculitis necrotizing
Gastrointestinal disorders	
Common:	Nausea
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, erythema multiforme
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

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.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA07
Telmisartan and Hydrochlorothiazide is a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Telmisartan and Hydrochlorothiazide 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.

Clinical efficacy and safety

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-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.

Cardiovascular prevention

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.
Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure,

hypotension and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

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.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. For more detailed information, see above under the heading “Cardiovascular prevention”. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Telmisartan and Hydrochlorothiazide in all subsets of the paediatric population in hypertension.

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. Telmisartan does not accumulate significantly in plasma on repeated administration.
Hydrochlorothiazide: Following oral administration of Telmisartan and Hydrochlorothiazide 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 ^{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.

Linearity/non-linearity

Telmisartan: 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.
Hydrochlorothiazide exhibits linear pharmacokinetics.

Elderly

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.

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 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.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
TELDAY H is available in strip of 10 Tablets.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C, protected from light and moisture.

MARKETED BY

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