Natrapharm

℞

Telmisartan + Hydrochlorothiazide

Telatraz®Plus

40mg/12.5mg Tablet
80mg/12.5mg Tablet
80mg/25mg Tablet
Angiotensin II Receptor Blocker (ARB) / Diuretic

1 FORMULATION

Telmisartan/Hydrochlorothiazide 40mg/12.5mg Tablet
Each uncoated tablet contains:
Telmisartan 40mg
Hydrochlorothiazide........................ 12.5mg

Telmisartan/Hydrochlorothiazide 80mg/12.5mg Tablet
Each uncoated tablet contains:
Telmisartan........................ 80mg
Hydrochlorothiazide........................ 12.5mg

Telmisartan/Hydrochlorothiazide 80mg/25mg Tablet
Each uncoated tablet contains:
Telmisartan.. .... 80mg
Hydrochlorothiazide........................ 25mg

2 PHARMACEUTICAL FORM

40mg + 12.5mg Tablets: Oblong shaped, biconvex, bilayered, uncoated tablets with one white to off-white color layer and one pink color mottled layer debossed with 'L199'. White to off white color layer may contain pink color specks.
80mg + 12.5mg Tablets: Oblong shaped, biconvex, bilayered, uncoated tablets with one white to off-white color layer and one pink color mottled layer debossed with 'L200'. White to off white color layer may contain pink color specks.
80mg + 25mg Tablets: Oblong shaped, biconvex, bilayered with one white to off-white color layer and one yellow color layer tablet.

3 PHARMACOLOGICAL PROPERTIES

3.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Angiotensin II Antagonists and Diuretics
ATC code: C09DA07

Mechanism of action
TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 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 TABLET once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan: Telmisartan is an orally effective and specific angiotensin II receptor (type 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.

In man, an 80 mg dose of telmisartan 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:
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 re-absorption, 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 hydrochlorothiazides, 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.

3.2 PHARMACOKINETIC PROPERTIES
Concomitant administration of hydrochlorothiazide and telmisartan has no effect on the pharmacokinetics of either drug.

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

Biotransformation and 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.

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. Total plasma clearance of telmisartan after oral administration is > 1500 ml/min. Terminal elimination half-life was > 20 hours.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged drug in urine. About 60% of the oral dose are eliminated as unchanged drug within 48 hours. Renal clearance is about 250 - 300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10 - 15 hours.

Elderly patients:
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.

Patients with 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.

Patients with 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.

4 CLINICAL PARTICULARS
4.1 INDICATIONS
Treatment of essential hypertension.

As fixed dose combination TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

4.2 RECOMMENDED DOSAGE
Adults
TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET should be taken once daily. The dose of telmisartan could be up-titrated before switching to TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET. Direct change from monotherapy to the fixed combinations may be considered.

- TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 40/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 40 mg or hydrochlorothiazide.
- TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 80/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan 80 mg or by TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 40/12.5 mg.
- TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 80 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan and Hydrochlorothiazide tablets 80 mg/12.5 mg.

The maximum antihypertensive effect is generally attained with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 4 - 8 weeks after the start of treatment.

When necessary, TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET may be administered with another antihypertensive drug.

In patients with severe hypertension treatment with telmisartan at doses up to 160 mg alone and in combination with hydrochlorothiazide 12.5 - 25 mg daily was well tolerated and effective.

TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET may be taken with or without food.

Renal impairment
Due to the hydrochlorothiazide component, TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET should not be used in patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised.

Hepatic impairment
In patients with mild to moderate hepatic impairment the posology should not exceed TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 40/12.5 mg once daily. TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

Elderly
No dosage adjustment is necessary.

Children and adolescents
Safety and efficacy of TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET have not been established in children and in adolescents up to 18 years.

4.3 ROUTE OF ADMINISTRATION
Solid Oral

4.4 CONTRAINDICATIONS
- Hypersensitivity to the active ingredient, to any of the excipients, or to other sulphonamide-derived substances (hydrochlorothiazide is a sulphonamide-derived substance).
- Second and third trimesters of pregnancy
- Lactation
- Choleastasis 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 TABLET with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated (please refer to "warnings and precautions").

4.5 WARNINGS AND PRECAUTIONS
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 anti-hypertensive 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 TABLET 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.

TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 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 TABLET 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 transplant:
TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET must not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see Contraindications).

There is no experience regarding the administration of TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET in patients with severe renal impairment or with a recent kidney transplant. Experience with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET 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 volume depletion:
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 TABLET.

Dual blockade of the renin-angiotensin-aldosterone system:
As a consequence of inhibiting the renin-angiotensin-aldosterone system 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 adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor antagonist) should therefore be limited to individually defined cases with close monitoring of renal function (see Contraindications).

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 other 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 TABLET 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. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. 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 TABLET, 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 (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest 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 ACTH. Conversely, due to the antagonism of the angiotensin II (AT1) receptors by the telmisartan component of TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus.

Lactose monohydrate
The maximum recommended daily dose of telmisartan/hydrochlorothiazide contains 84 mg of lactose monohydrate in the dose strength 40/12.5 mg, 180.5 mg in the dose strength 80/12.5 mg, and 169.4 mg of lactose monohydrate in the dose strength 80/25 mg.

Patients with rare hereditary condition of galactose intolerance e.g. galactosaemia should not take this medicine.

Mannitol
The maximum recommended daily dose of telmisartan and hydrochlorothiazide combination tablet contains 170 mg mannitol in the dose strength 40/12.5 mg and 340 mg mannitol in the dose strengths 80/12.5 mg and 80/25 mg.

Patients with rare hereditary condition of fructose intolerance should not take this medicine.

Sodium- and/or volume-depleted patients

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan and Hydrochlorothiazide Tablet.

Diabetes mellitus:
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET.

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.

Acute Myopia and Secondary 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.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry (see Side Effects). Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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.

Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

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. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

4.6 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF 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/HCTZ). Coadministration of lithium and telmisartan/HCTZ 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 HCTZ-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of HCTZ 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 HCTZ-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.

Summary of product Characteristics
Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when telmisartan/HCTZ 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. In Published Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Antidiabetic medicinal products (oral agents and insulin)
Dose 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 HCTZ.

Cholestyramine and colestipol resins
Absorption of HCTZ is impaired in the presence of anionic exchange resins.

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

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol) Dose adjustment of uricosuric medications may be necessary as HCTZ may raise the level of serum uric acid. Increase in dose of probenecid or sulfinpyrazone may be necessary. Coadministration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts
Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dose adjusted accordingly.

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

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.

4.7 STATEMENT ON USAGE DURING PREGNANCY AND LACTATION
Effects on fertility
No studies on fertility in humans have been performed.

In non-clinical studies, an effect of telmisartan and hydrochlorothiazide on male and female fertility was not observed.

Use in pregnancy
Telmisartan:
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists exposure 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).

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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.

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester.

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.

Use in lactation.
TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET is contraindicated during lactation. It is not known whether telmisartan is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk. Thiazides appear in human milk and may inhibit lactation.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
The overall incidence of adverse events reported with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients receiving telmisartan plus hydrochlorothiazide (835) or telmisartan alone (636). There was no dose-relationship to undesirable effects and there was no correlation with gender, age or race of the patients.

Adverse reactions reported in clinical trials with telmisartan plus hydrochlorothiazide are shown below according to system organ class. Adverse reactions not observed in clinical trials with telmisartan plus hydrochlorothiazide but expected during treatment with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET based on the experience with telmisartan or hydrochlorothiazide alone have been included and are detailed in separate sections below:

Infections and infestations: Bronchitis, pharyngitis, sinusitis

Immune system disorders: Exacerbation or activation of systemic lupus erythematosus*
* based on post-marketing experience

Metabolism and nutrition disorders: Hypokalaemia, hyponatraemia, hyperuricaemia

Psychiatric disorders: Anxiety, depression

Nervous system disorders: Dizziness, syncope/faint, paraesthesia, sleep disturbances, insomnia

Eye disorders: Abnormal vision, transient blurred vision

Ear and labyrinth disorders: Vertigo

Cardiac disorders: Cardiac arrhythmias, tachycardia

Vascular disorders: Hypotension (including orthostatic hypotension)

Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders: Diarrhoea, dry mouth, flatulence, abdominal pain, constipation, dyspepsia, vomiting, gastritis

Hepato-biliary disorders: Abnormal hepatic function / liver disorder*
*Most cases of hepatic function abnormal / liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.

Skin and subcutaneous tissue disorders: Angiooedema (with fatal outcome), erythema, pruritus, rash, sweating increased, urticaria

Musculoskeletal, connective tissue and bone disorders:
Back pain, muscle spasm, myalgia, arthralgia, leg pain, cramps in legs

Reproductive system and breast disorders: Impotence

General disorders and administration site conditions:
Chest pain, influenza-like symptoms, pain

Investigations: Increase in uric acid, increase in creatinine, increase in liver enzymes, increase in blood creatine phosphokinase

4.9 TELMISARTAN:
Additional side effects reported in clinical trials with telmisartan monotherapy in the indication hypertension or in patients 50 years or older at high risk of cardiovascular events were as follows:

Infections and Infestations: Upper respiratory tract infections, urinary tract infections (including cystitis), sepsis including fatal outcome

Blood and lymphatic system disorders: Anaemia, thrombocytopenia, eosinophilia

Immune system disorders: Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders: Hyperkalaemia, hypoglycaemia (in diabetic patients)

Cardiac disorders: Bradycardia

Gastrointestinal disorders: Stomach upset

Skin and subcutaneous tissue disorders: Eczema, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders: Arthrosis, tendon pain (tendinitis like symptoms)

Renal and urinary disorders: Renal impairment including acute renal failure (see also under Special precautions and warnings)

General disorders and administration site conditions: Asthenia (weakness)

Investigations: Decrease in haemoglobin

4.10 HYDROCHLOROTHIAZIDE:
Additional side effects reported with hydrochlorothiazide monotherapy were as follows:

Infections and infestations: Sialadenitis

Neoplasms Benign, malignant and unspecified (incl. cysts and polyps):
Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma of skin or lip)

Blood and the lymphatic system disorders: Thrombocytopenia (sometimes with purpura), aplastic anaemia, haemolytic anaemia, bone marrow depression, leukopenia, neutropenia/agranulocytosis

Immune system disorders: Anaphylactic reactions, allergy

Endocrine disorders: Loss of diabetic control

Metabolism and nutrition disorders: Cause or exacerbate volume depletion, electrolyte imbalance, anorexia, loss of appetite, hyperglycaemia, hypercholesterolaemia, hypomagnesaemia, hypercalcaemia, hypochloraemic alkalosis

Psychiatric disorders: Restlessness

Nervous system disorders: Headache, light-headedness

Eye disorders: Xanthopsia, acute myopia, acute angle-closure glaucoma

Vascular disorders: Necrotizing angiitis (vasculitis)

Gastro-intestinal disorders: Nausea, stomach upset, pancreatitis

Hepato-biliary disorders: Jaundice (hepatocellular or cholestatic jaundice)

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, erythema multiforme, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, cutaneous vasculitis, photosensitivity reactions

Musculoskeletal, connective tissue and bone disorders: Weakness

Renal and urinary disorders: Interstitial nephritis, renal dysfunction, glycosuria

General disorders and administration site conditions: Fever

Investigations: Increase in triglycerides

4.11 OVERDOSE AND TREATMENT
Limited information is available for TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET with regard to overdose in humans.

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.

No specific information is available on the treatment of overdose with TELMISARTAN AND HYDROCHLOROTHIAZIDE TABLET. The patient should be closely monitored, and the treatment should be symptomatic and supportive depending on the time since ingestion and the severity of the symptoms. 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. Telmisartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 DOSAGE FORMS AND PACKAGING AVAILABLE
Solid Oral
Alu/Alu Blister Pack x 10's (Box of 30's)

6 STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.

Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

7 MANUFACTURED BY:
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8 REGISTRATION NUMBER:
40mg/12.5mg-DR-XY49218;
80mg/12.5mg-DR-XY49217;
80mg/25mg-DR-XY49216

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