Telarb®-H

(Telmisartan + Hydrochlorothiazide)

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

1. NAME OF THE PRODUCT

Telarb®-H (Telmisartan + Hydrochlorothiazide) Tablet 40mg /12.5mg
Telarb®-H (Telmisartan + Hydrochlorothiazide) Tablet 80mg /12.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Telarb®-H Tablet 40mg / 12.5mg
Each bilayered tablet contains:
Telmisartan USP……..…40mg
Hydrochlorothiazide BP.....12.5mg

Telarb®-H Tablet 80mg / 12.5mg
Each bilayered tablet contains:
Telmisartan USP……..…80mg
Hydrochlorothiazide BP.....12.5mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:
Telarb®-H Tablet 40mg / 12.5mg: White to off-white coloured (layer of Telmisartan) and yellow coloured (layer of Hydrochlorothiazide), oblong shaped bilayered tablet, plain from both sides.
Telarb®-H Tablet 80mg / 12.5mg: White to off-white coloured (layer of Telmisartan) and pink coloured (layer of Hydrochlorothiazide), oblong shaped bilayered tablet, plain from both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Treatment of essential hypertension.
Telarb®-H fixed dose combination (40mg telmisartan/12.5mg hydrochlorothiazide and 80mg telmisartan/12.5mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Telarb®-H 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.

- **Telarb®-H** 40mg/12.5mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 40mg.
- **Telarb®-H** 80mg/12.5mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 80mg.

Special populations:

Renal impairment: Periodic monitoring of renal function is advised.

Hepatic impairment: In patients with mild to moderate hepatic impairment the posology should not exceed **Telarb®-H** 40mg/12.5mg once daily. **Telarb®-H** 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.

Paediatric population: The safety and efficacy of **Telarb®-H** in children and adolescents aged below 18 have not been established. No data are available.

Method of administration:

Telarb®-H 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: **Telarb®-H** 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.
- 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 < 30ml/min), anuria.
- Refractory hypokalaemia, hypercalcaemia.
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2)

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Pregnancy: Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment: Telmisartan/ 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/ 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/ 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/ Hydrochlorothiazide should not be used in patients with severe renal impairment (creatinine clearance <30ml/min). There is no experience regarding the administration of Telmisartan/ Hydrochlorothiazide in patients with recent kidney transplantation. Experience with Telmisartan/ 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.

Volume and/or sodium depleted patients: Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of Telmisartan/ Hydrochlorothiazide. Isolated cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) have been observed with the use of hydrochlorothiazide.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor

blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system: In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism: Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Telmisartan/ 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 patient's 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 12.5mg dose contained in Telmisartan/ 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/ Hydrochlorothiazide, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan/ Hydrochlorothiazide, 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/ Hydrochlorothiazide.
- ***Hyponatraemia and hypochloraemic alkalosis:*** There is no evidence that Telmisartan/ 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 blockers telmisartan is apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

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

General: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics, including hydrochlorothiazide. Cases of photosensitivity reactions have been reported with thiazide diuretics. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal effusion, Acute Myopia and Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia

and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle- closure glaucoma may include a history of 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. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC

Acute Respiratory Toxicity: Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Telmisartan/ Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Intestinal angioedema: Intestinal angioedema has been reported in patients treated with angiotensin II receptor blockers. These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor blockers. If intestinal angioedema is diagnosed, Telmisartan 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:

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 blockers (including Telmisartan/ Hydrochlorothiazide). Co-administration of lithium and Telmisartan/

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.

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

Medicinal products that may increase potassium levels or induce hyperkalaemia: (e.g. ACE inhibitors, potassium sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine or other medicinal products such as heparin sodium). If these medicinal products are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the reninangiotensin 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/ 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (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 favors 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. 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 blockers. 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 blockers 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.

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.

4.6. FERTILITY, PREGNANCY AND LACTATION:

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

Pregnancy: There are no adequate data from the use of Telmisartan/ Hydrochlorothiazide in pregnant women. Studies in animals have shown reproductive toxicity. Unless continued angiotensin II receptor blocker 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to angiotensin II receptor blocker 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 blockers should be closely observed for hypotension. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding: Because no information is available regarding the use of Telmisartan/ Hydrochlorothiazide during breast-feeding, Telmisartan/

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. If Telmisartan/ Hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

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

4.8. UNDESIRABLE EFFECTS:

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).

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:
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

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 blockers (ARBs) and diuretics.

ATC code: C09DA07

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

Mechanism of action:

Telmisartan:

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) blocker.

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 characterized 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.

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 reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma rennin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the reninangiotensin-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.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption:

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 – 1.5h after dosing. The absolute bioavailability of telmisartan at 40mg and 160mg 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 40mg tablet and about 19% after a 160mg 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/ 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 – 1.14l/kg.

Metabolism:

Telmisartan is metabolized 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 metabolized 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 >1500ml/min. Terminal elimination half-life was >20 hours.

Hydrochlorothiazide: 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 – 300ml/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 – 160mg with greater than proportional increases of

plasma concentrations (C_{max} and AUC) with increasing doses. ***Hydrochlorothiazide:*** Hydrochlorothiazide exhibits linear pharmacokinetics.

5.3. PRECLINICAL SAFETY DATA:

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

Toxicological findings also well known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers 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 effects of telmisartan on male or female fertility were observed.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Telarb®-H Tablet 40mg / 12.5mg:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets
- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Yellow Iron Oxide
- Colloidal Silicon Dioxide

Telarb®-H Tablet 80mg / 12.5mg:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets
- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Red Iron Oxide Color
- Silicon Dioxide Fumed

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

6.5. NATURE AND CONTENTS OF CONTAINER:

Telarb®-H Tablet 40mg / 12.5mg: Alu/Alu blister packing, pack size is 14's.
Telarb®-H Tablet 80mg / 12.5mg: Alu/Alu blister packing, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Telarb®-H Tablet 40mg / 12.5mg: USP Specs.
Telarb®-H Tablet 80mg / 12.5mg: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

Telarb®-H Tablet 40mg / 12.5mg: 100513
Telarb®-H Tablet 80mg / 12.5mg: 100514

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Telarb®-H Tablet 40mg / 12.5mg: 19th December, 2019
Telarb®-H Tablet 80mg / 12.5mg: 19th December, 2019

10. DATE OF REVISION OF THE TEXT

ٹیل آرب®-ایچ ٹیبلٹ

(ٹیلمیسارٹن + ہائیڈروکلوروتھائیزائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔