MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.1 Name of the medicinal product:

TELSARTAM -HCT 80/10/12.5

1.2 (Invented) name of the medicinal product:

Generic Name/INN Name:

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets

1.2 Strength:

Each bilayer uncoated tablet contains

Telmisartan USP	80 mg
Amlodipine Besylate USP	
Equivalent to Amlodipine	10 mg
Hydrochlorothiazide USP	12.5 mg
Excipients	Q. S

Colour: Yellow Oxide of Iron

1.3 Pharmaceutical form:

Oral solid dosage form- Bilayer Uncoated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specifi-cation	Label Claim (mg)	Std Qty./ Tablet (mg)	%w/w	Function
Layer 1						
Granulation						
1	Lactose Monohydrate	BP	--	289.20	48.20	Diluent
Top Spray granulation						
2	Telmisartan	USP	80.00	80.000	13.33	API
3	Povidone K -30	BP	--	6.000	1.00	Binder
4	Sodium Hydroxide	BP	--	6.800	1.13	Basifying Agent
5	Meglumine	USP	--	18.000	3.00	Basifying

						Agent
6	Purified Water	BP	--	q.s.	N.A	Vehicle
Lubrication						
7	Sodium Stearyl Fumarate	BP	--	10.00	1.67	Lubricant
Weight of Telmisartan layer				410.00	68.33	
Layer 2						
Dry Mixing						
8	Amlodipine Besylate Eq. to Amlodipine	USP	10.00	13.900	2.32	API
9	Hydrochlorothiazide	USP	12.50	12.500	2.08	API
10	Microcrystalline cellulose PH 102	BP	--	136.30	22.71	Diluent
11	Pregelatinised Starch	BP	--	25.000	4.17	Dry Binder
12	Iron oxide yellow	USP	--	1.000	0.17	Colorant
13	Colloidal Anhydrous Silica	BP	--	0.300	0.05	Disintegrant
Lubrication						
14	Magnesium Stearate	BP	--	1.000	0.17	Lubricant
Weight of Amlodipine & Hydrochlorothiazide layer				190.00	31.66	
Total weight of Bilayer uncoated Tablet				600.00	100.0	

3. Pharmaceutical form:

Dosage Form: Oral solid dosage form- Bilayer Uncoated Tablet

Visual & Physical characteristics of the product:

White to off-white and yellow colored, bilayer, capsule shape, uncoated tablets, and plain on both sides. White colour layer may contain yellow colour specks.

4. Clinical particulars

4.1. Therapeutic indications:

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is indicated for the treatment of essential hypertension in adults. This fixed combination drug is not indicated for the initial therapy of hypertension.

4.2. Posology and method of administration:

Posology

The usual dose is one tablet once daily. The dosage may be increased to two tablets once daily after two weeks of therapy. The maximum recommended dose of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets. Telmisartan, Amlodipine and Hydrochlorothiazide Tablets may be administered with or without food.

Add-on/ Switch Therapy

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets may be used for patients not adequately controlled on any two of the following antihypertensive classes: ARBs, calcium channel blockers, and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets may be switched to Telmisartan, Amlodipine and Hydrochlorothiazide Tablets containing a lower dose of that component to achieve similar BP reductions.

Replacement Therapy

Patients receiving telmisartan, hydrochlorothiazide and amlodipine from separate tablets can instead receive tablets of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets containing the same component doses in one tablet once daily.

Specific Populations

Renal Impairment

No initial dosage adjustment is required for patients with mild or moderate renal impairment. Safety and effectiveness of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets in patients with severe renal impairment (creatinine clearance ≤30 mL/min) have not been established. In patients with severe renal impairment, Telmisartan, Amlodipine and Hydrochlorothiazide Tablets are not recommended.

Hepatic Impairment

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders

or hepatic impairment should have treatment started with Telmisartan, Amlodipine and Hydrochlorothiazide Tablets under close medical supervision

Patients 75 Years of Age and Older

Patients ≥ 75 years of age should start amlodipine at 2.5 mg, therefore initial therapy with Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is not recommended in patients > 75 years old.

Pediatric Use

The safety and effectiveness of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets in pediatric patients have not been established.

Method of Administration

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

4.3. Contraindications:

Telmisartan /hydrochlorothiazide/amlodipine is contraindicated in patients with known hypersensitivity to telmisartan, hydrochlorothiazide or amlodipine or any other component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Cholestasis and biliary obstructive disorders.

Severe hepatic impairment.

Severe renal impairment (creatinine clearance≤30 ml/min

Refractory hypokalemia, hypercalcemia.

Second and third trimesters of pregnancy

Biliary obstructive disorders and severe hepatic impairment. Shock (including cardiogenic shock). Obstruction of the outflow tract of the left ventricle (e.g. high-grade aortic stenosis). Hemodynamically unstable heart failure after acute myocardial infarction Do not co-administer aliskiren with telmisartan /hydrochlorothiazide/amlodipine in patients with diabetes.

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4.4. Special warnings and precautions for use:

Pregnancy

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

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia

Hepatic Impairment

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

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Telmisartan, Amlodipine and Hydrochlorothiazide Tablets should therefore be used with caution in these patients.

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 (RAAS)

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Renal Impairment and Kidney Transplantation

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia, or acute renal failure on Telmisartan, Amlodipine and Hydrochlorothiazide Tablets. When Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular Hypovolaemia

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of telmisartan. If hypotension occurs with Telmisartan, Amlodipine and Hydrochlorothiazide Tablets, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

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 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.

Unstable Angina Pectoris, Acute Myocardial Infarction

There are no data to support the use of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with Cardiac Failure

In an amlodipine long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Therefore, patients with heart failure should be treated with caution. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Elderly Patients

The increase of the amlodipine dosage should take place with care in the elderly patients.

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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 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 angleclosure glaucoma may include a history of sulfonamide or penicillin allergy.

Hypersensitivity Reaction

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

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus Erythematosus

Non-melanoma Skin Cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.

Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Post Sympathectomy Patients

The antihypertensive effects of hydrochlorothiazide may be enhanced in the post sympathectomy patient.

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 12.5 mg 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 (AT1) receptors by the telmisartan component of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets, hyperkalaemia might occur. Risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassiumsparing diuretics, potassium supplements or potassium-containing salt substitutes should be coadministered cautiously with Telmisartan, Amlodipine and Hydrochlorothiazide Tablets.

Hyponatraemia and hypochloraemic alkalosis

There is no evidence that telmisartan/amlodipine/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.

4.5. Interaction with other medicinal products and other forms of interaction:

Drug Interactions

No drug interaction studies have been performed.

To be taken into account with concomitant use

Other Antihypertensive Medicinal Products

The blood pressure lowering effect of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets can be increased by concomitant use of other antihypertensive medicinal products.

Medicinal Products with Blood Pressure Lowering Potential

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (Systemic Route)

Reduction of the antihypertensive effect

Interactions linked to Telmisartan

Concomitant use not recommended

Potassium Sparing Diuretics or Potassium Supplements Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with thiazide diuretics or angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other Antihypertensive Agents Acting on the Renin-Angiotensin-Aldosterone System (Raas)

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.

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 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. 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.

Concomitant Use Requiring Caution

Non-Steroidal Anti-Inflammatory Medicinal Products NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and nonselective NSAIDs) may reduce the antihypertensive effect 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 medicinal products 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. Ramipril 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 known.

Concomitant use to be taken into account

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

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 Inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required

CYP3A4 Inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). Dantrolene (Infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Grapefruit and Grapefruit Juice

Administration of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects

Concomitant use to be taken into account

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully

understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Mechanistic Target of Rapamycin (MTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on Telmisartan, Amlodipine and Hydrochlorothiazide Tablets to 20 mg daily

Interactions linked to Hydrochlorothiazide

Antidiabetic Drug

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 hydrochlorothiazide.

Cholestyramine and Colestipol Resins

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

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 events 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.

Non-Steroidal Anti-Inflammatory Medicinal Products

Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Therefore, when hydrochlorothiazide and non-steroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

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.

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

Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dose of probenecid or sulfinpyrazone may be necessary

Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

Use in Special Population

Patients with Renal Impairment

Safety and effectiveness of telmisartan/amlodipine/hydrochlorothiazide in patients with severe renal impairment (CrCl ≤30 mL/min) have not been established. In patients with severe renal impairment, Telmisartan, Amlodipine and Hydrochlorothiazide Tablets are not recommended. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60 mL/min) renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using in such patients as amlodipine and telmisartan are not dialyzable

Patients with Hepatic Impairment

Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is contraindicated in patients with severe hepatic impairment.

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance and higher blood levels, patients with biliary obstructive disorders or hepatic insufficiency should initiate treatment under close medical supervision using the Telmisartan, Amlodipine and Hydrochlorothiazide Tablets

In addition, Telmisartan, Amlodipine and Hydrochlorothiazide Tablets should be used with caution in patients with impaired hepatic function or progressive liver disease as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

LACTATION

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Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is contraindicated in patients with severe hepatic impairment. As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance and higher blood levels, patients with biliary obstructive disorders or hepatic insufficiency should initiate treatment under close medical supervision using the Telmisartan, Amlodipine and Hydrochlorothiazide Tablets

In addition, Telmisartan, Amlodipine and Hydrochlorothiazide Tablets should be used with caution in patients with impaired hepatic function or progressive liver disease as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease

Pregnant Women

There are limited data from the use of telmisartan/ amlodipine/ hydrochlorothiazide in pregnant women

Telmisartan

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

Studies with telmisartan 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 medicinal products. 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.

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.

PEDIATRIC USE

Safety and effectiveness in paediatric patients has not been established.

Hydrochlorothiazide

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.

Lactating Women

Because no information is available regarding the use of telmisartan during breast-feeding, Telmisartan, Amlodipine and Hydrochlorothiazide Tablets is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of hydrochlorothiazide during breast feeding is not recommended. If

hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

PEDIATRIC USE

Safety and effectiveness in paediatric patients have not been established. Neonates with a History of In-Utero Exposure to Combination If oliguria or hypotension occurs, attention should be directed towards support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

GERIATRIC USE

No overall differences in effectiveness and safety, were observed in these patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

4.7. Effects on ability to drive and use machines:

This medicinal product has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8. Undesirable effects:

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients). Adverse

reactions previously reported with one of the individual components (telmisartan, amlodipine and hydrochlorothiazide) may be potential adverse reactions with telmisartan/amlodipine/hydrochlorothiazide as well, even if not observed in clinical trials or during the post-marketing period.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

Not Known				Anaphylactic reactions, hypersensitivity
Endocrine disorders				
Not Known				Diabetes mellitus inadequate control
Metabolism and nutrition disorders				
Common				Hypoma gnesaemia
Uncommon	Hypokalemia	Hyperkalaemia		
Rare	Hyperuri caemia, hyponatraemi a	hypoglycaemia (in diabetic patients)		Hypercalcaemia
Very rare			hyperglycaem ia	Hypochlorae micalkalosis
Not Known				Anorexia, appetite decreased, electrolyte imbalance, Hypercholester o laemia hyperglycaemia , hypovolaemia
Psychiatric disorders				
Uncommon			mood change	
Rare	depression, anxiety, insomnia		confusion	
Not Known				Restlessness
Nervous system disorders				
Common	dizziness			
Uncommon	somnolence, migraine, headache, paraesthesia			

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Rare	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor Insomnia, sleep disorders			Headache
Very rare			extrapyramidal syndrome, hypertonia	
Not Known				Light-headedness
Eye disorders				
Common			visual disturbance (including diplopia)	
Uncommon			visual impairment	
Rare	vision blurred Visual disturbance,	visual disturbance		
Not Known				Xanthopsia, choroidal effusion, acute myopia, acute angle-closure glaucoma
Ear and labyrinth disorders				
Uncommon	vertigo		tinnitus	
Cardiac disorders				
Uncommon	Tachycardia bradycardia, palpitations arrhythmias	Bradycardia		
Rare		Tachycardia		
Very rare			myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation	
Vascular disorders				
Uncommon	hypotension, orthostatic hypotension, flushing			
Very rare			vasculitis	
Not Known				Vasculitis necrotizing
Respiratory, thoracic and mediastinal disorders				
Uncommon	cough	dyspnea	dyspnoea, rhinitis	

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Rare	Respiratory distress (including pneumonitis and pulmonary oedema)			
Very rare	interstitial lung disease[3]			
Gastrointestinal disorder				
Common				Nausea
Uncommon	abdominal pain, diarrhoea, nausea	Flatulence	altered bowel habits (including diarrhoea and constipation)	
Rare	vomiting, gingival hypertrophy, dyspepsia, dry mouth Abdominal pain, constipation, dyspepsia, vomiting, gastritis	stomach discomfort		
Very rare			pancreatitis, gastritis	
Not Known				Pancreatitis, stomach discomfort
Hepato-biliary disorders				
Rare		hepatic function abnormal, liver disorder[2]		
Very rare			hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)	
Not Known				Jaundice hepatocellular, jaundice cholestatic
Skin and subcutaneous tissue disorders				
Uncommon	pruritus	Hyperhidrosis	alopecia, purpura, skin discolouration, hyperhidrosis	
Rare	eczema, erythema, rash	angioedema (with fatal outcome), drug eruption, toxic skin eruption,urticaria		

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Very rare			angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity	
Not known			toxic epidermal necrolysis	Lupus-like syndrome, photosensitivity reactions, skin vasculitis, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders				
Common			ankle swelling	
Uncommon	arthralgia, muscle spasms (cramps inlegs), myalgia			
Rare	back pain, pain in extremity (leg pain)	Arthrosis, tendon pain (tendinitis like symptoms)		
Not Known				Weakness
Renal and urinary disorders				
Uncommon		renal impairment including acute renal failure	micturition disorder, pollakiuria	
Rare	nocturia			
Not Known				Nephritis interstitial, renal dysfunction, glycosuria
Reproductive system and breast disorders				
Uncommon	erectile dysfunction		Gynaecomastia	
General disorders and administration site condition				
Common	peripheral oedema			
Uncommon	asthenia, chest pain, fatigue, oedema		Pain	
Rare	malaise	influenza-like illness		
Not Known				Pyrexia
Investigations				
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased	

Rare	blood uric acidincreased	blood creatine phosphokinase increased, haemoglobin decreased		
Not Known				Triglycerides increased

4.9. Overdose:

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/Kg in both mice and rats

Treatment

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 of both telmisartan and amlodipine. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2

hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Telmisartan and Amlodipine are not removed by haemodialysis.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Angiotensin receptor blocker & calcium channel blocker

ATC code: Telmisartan - C09CA07; Amlodipine – C08CA01; Hydrochlorothiazide – C03AA03

Telmisartan is a non-peptide ARB. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There is also an angiotensin type 2 (AT2) receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3000-fold) for the AT1 receptor than for the AT2 receptor. Telmisartan does not inhibit the ACE (kininase II) nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity (PRA) and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac

muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in PRA, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood

Pharmacodynamic properties:

The active ingredients of Telmisartan, Amlodipine and Hydrochlorothiazide Tablets target three separate mechanisms involved in blood pressure (BP) regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; telmisartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle,

adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume.

Telmisartan

Telmisartan is an orally active 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 reactions. In humans, 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. 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 to 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 trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent. In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and

natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of substances 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 pretreatment 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. Two large randomised, controlled trials (ONTARGET (ON going 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. 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout

Use in Patients with Heart Failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology. A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure. In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings

suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in PRA, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an ARB tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood. After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours

5.2. Pharmacokinetic properties:

Absorption

Telmisartan

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. 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 Telmisartan is highly bound to plasma proteins (more than 99.5%), mainly albumin and alpha1 -acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding.

Amlodipine

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Hydrochlorothiazide

Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83-1.14 l/kg. Hydrochlorothiazide crosses the placenta, but not the blood-brain barrier and is excreted in breast milk.

Metabolism

Telmisartan

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 human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Amlodipine

Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

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Hydrochlorothiazide

Hydrochlorothiazide is not metabolized.

Elimination

Telmisartan

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (more than 97%) was eliminated unchanged in the feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Total plasma clearance of telmisartan is more than 800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Amlodipine

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Hydrochlorothiazide

Hydrochlorothiazide eliminated rapidly by the kidneys. Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. At least 61% of the oral dose is eliminated unchanged within 24 hours. About 60% of the oral dose is eliminated within48 hours. Renal clearance is about 250-300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10-15 hours.

Linearity/Non-Linearity

The small reduction in AUC for telmisartan is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. Cmax and to a lesser extent AUC increase disproportionately at doses above 40 mg. Amlodipine exhibits linear pharmacokinetics.

Special Populations

Renal Impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, lower plasma concentrations

were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

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

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic impairment can be expected to have reduced clearance. In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.

Paediatric Population (Age Below 18 Years)

No pharmacokinetic data are available in the paediatric population.

Geriatric Population

The pharmacokinetics of telmisartan do not differ in young and elderly patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half life

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

5.3 Preclinical safety data

Animal Toxicology or Pharmacology

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

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

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

Amlodipine

Reproductive Toxicology Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of Fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 10 mg/day on an mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis and Mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. *Based on patient weight of 50 kg

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained in the in vitro CHO Sister Chromatid Exchange (clastogenicity) assay, in the Mouse Lymphoma Cell (mutagenicity) assay, and in the Aspergillus nidulans non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

6. Pharmaceutical particulars:

6.1. List of Excipients:

- Lactose Monohydrate
- Povidone K -30
- Sodium Hydroxide
- Meglumine
- Sodium stearyl fumarate
- Microcrystalline cellulose PH 102
- Pregelatinised Starch
- Iron oxide yellow
- Colloidal Anhydrous Silica
- Magnesium Stearate

6.2. Incompatibilities:

Not applicable.

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store at temperature not exceeding 30°C Protect from light & moisture.

1.3.1.6.5. Nature and contents of container:

Primary Pack: 7 Tablets are packed in 1 Alu-Alu blister pack.

Secondary Pack: Such 4 blisters are packed in one mono carton along with package insert.

1.3.1.6.6. Special precautions for disposal:

No special requirements.

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

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

7. Applicant

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