Telarb®-Plus

(Telmisartan + Amlodipine Besylate)

1. NAME OF THE PRODUCT

Telarb®-Plus (Telmisartan + Amlodipine Besylate) 40mg/5mg Tablet
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Telarb®-Plus (Telmisartan + Amlodipine Besylate) 80mg/5mg Tablet
Telarb®-Plus (Telmisartan + Amlodipine Besylate) 80mg/10mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Telarb®-Plus 40mg/5mg Tablet
Each bilayered tablet contains:
Telmisartan USP.....40mg
Amlodipine Besylate Ph. Eur. eq. to Amlodipine.....5mg

Telarb®-Plus 40mg/10mg Tablet
Each bilayered tablet contains:
Telmisartan USP.....40mg
Amlodipine Besylate Ph. Eur. eq. to Amlodipine.....10mg

Telarb®-Plus 80mg/5mg Tablet
Each bilayered tablet contains:
Telmisartan USP.....80mg
Amlodipine Besylate Ph. Eur. eq. to Amlodipine…….5mg

Telarb®-Plus 80mg/10mg Tablet
Each bilayered tablet contains:
Telmisartan USP.....80mg
Amlodipine Besylate Ph. Eur. eq. to Amlodipine….10mg

3. PHARMACEUTICAL FORM

Tablet

Appearance:
Telarb®-Plus 40mg/5mg Tablet: Green colored (upper layer of Amlodipine) and off white colored (lower layer of Telmisartan) oval shaped bilayered tablet, plain from both sides.
Telarb®-Plus 40mg/10mg Tablet: Yellow colored (upper layer of Amlodipine) and off white colored (lower layer of Telmisartan) oval shaped bilayered tablet, plain from both sides.

Telarb®-Plus 80mg/5mg Tablet: Green colored (upper layer of Amlodipine) and off white colored (lower layer of Telmisartan) oblong shaped bilayered tablet, plain from both sides.

Telarb®-Plus 80mg/10mg Tablet: Yellow colored (upper layer of Amlodipine) and off white colored (lower layer of Telmisartan) oblong shaped bilayered tablet, plain from both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Treatment of essential hypertension in adults:

Add on therapy: **Telarb®-Plus** is indicated in adults whose blood pressure is not adequately controlled on amlodipine alone.

Replacement therapy: Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of **Telarb®-Plus** containing the same component doses.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology:

The recommended dose of this medicinal product is one tablet per day. The maximum recommended dose is one tablet 80mg telmisartan/10mg amlodipine per day. This medicinal product is indicated for long term treatment. Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Add on therapy:

Telarb®-Plus *40mg/5mg Tablets:* **Telarb®-Plus** 40mg/5mg may be administered in patients whose blood pressure is not adequately controlled on amlodipine 5mg alone.

Telarb®-Plus *40mg/10mg Tablets:* **Telarb®-Plus** 40mg/10mg may be administered in patients whose blood pressure is not adequately controlled on amlodipine 10mg alone.

Telarb®-Plus *80mg/5mg Tablets:* **Telarb®-Plus** 80mg/5mg may be administered in patients whose blood pressure is not adequately controlled on **Telarb®-Plus** 40mg/5mg.

Telarb®-Plus *80mg/10mg Tablets:* **Telarb®-Plus** 80mg/10mg may be administered in patients whose blood pressure is not adequately controlled on **Telarb®-Plus** 40mg/10mg or **Telarb®-Plus** 80mg/5mg.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered. Patients treated with 10mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to **Telarb®-Plus**

40mg/5mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy: Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Telarb®-Plus containing the same component doses in one tablet once daily.

Elderly (> 65 years): No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients. Normal amlodipine dose regimens are recommended in the elderly, but increase of dose should take place with care.

Renal impairment: Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using telmisartan/amlodipine in such patients as amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment: Telarb®-Plus is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment telmisartan/amlodipine should be administered with caution. For telmisartan the posology should not exceed 40mg once daily.

Paediatric population: The safety and efficacy of telmisartan/amlodipine in children aged below 18 years have not been established. No data are available.

Method of administration:

- For oral use only.
- Telarb®-Plus can be taken with or without food. It is recommended to take Telarb®-Plus with some liquid.
- Telarb®-Plus 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 the active substances, to dihydropyridine derivatives, or to any of the excipients.
- 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).
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan/amlodipine with aliskiren-containing medicinal 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 is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose 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 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).

Renal impairment and kidney transplantation: When telmisartan/amlodipine 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 in patients with a recent kidney transplant. Amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable.

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 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, 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 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.

Diabetic patients treated with insulin or antidiabetics: In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

Hyperkalemia: The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia. Hyperkalaemia may be fatal in the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events. Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke

hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extensive trauma).

Serum potassium should be monitored closely in these patients.

Elderly patients: The increase of the amlodipine dose should take place with care in the elderly patients.

Sodium: This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

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

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 FORM OF INTERACTIONS:

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions linked to the combination: 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 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 blockers 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 angiotensin converting enzyme inhibitors, and with angiotensin II receptor blockers, 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): 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.

Concomitant use requiring caution:

Non-steroidal anti-inflammatory medicinal products: NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dose regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect 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 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: The co-administration of telmisartan and ramipril led to an increase of up to 2.5-fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

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): 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 amlodipine 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.

Ciclosporin: No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporin were observed. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin 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 10mg of amlodipine with simvastatin 80mg resulted in an increase in exposure to simvastatin up to 77% compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20mg daily.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: No data from controlled clinical studies with the fixed dose combination or with the individual components are available.

Pregnancy: There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Breast-feeding: 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. Because no information is available regarding the use of telmisartan during breast-feeding, telmisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Telmisartan / Amlodipine has moderate influence on the ability to drive and use machines. When driving vehicles or operating machinery it should be taken into account that syncope, somnolence, dizziness, or vertigo may occasionally occur when taking antihypertensive therapy. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

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 (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Telmisartan / Amlodipine	Telmisartan	Amlodipine
Infections and infestations			
Uncommon		upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis	
Rare	cystitis	sepsis including fatal outcome	

Blood and lymphatic system disorders:			
Uncommon		anaemia	
Rare		thrombocytopenia, eosinophilia	
Very rare			leukocytopenia, thrombocytopenia
Immune system disorders:			
Rare		hypersensitivity, anaphylactic reaction	
Very rare			hypersensitivity
Metabolism and nutrition disorders			
Uncommon		hyperkalaemia	
Rare		hypoglycaemia (in diabetic patients), hyponatraemia	
Very rare			hyperglycaemia
Psychiatric disorders			
Uncommon			mood change
Rare	depression, anxiety, insomnia		confusion
Nervous system disorders			
Common	dizziness		
Uncommon	somnolence, migraine, headache, paraesthesia		
Rare	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor		
Very rare			extrapyramidal syndrome, hypertonia

Eye disorders			
Common			visual disturbance (including diplopia)
Uncommon			visual impairment
Rare		visual disturbance	
Ear and labyrinth disorders			
Uncommon	vertigo		tinnitus
Cardiac disorders			
Uncommon	bradycardia, palpitations		
Rare		tachycardia	
Very rare			myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders			
Uncommon	hypotension, orthostatic hypotension, flushing		
Very rare			vasculitis
Respiratory, thoracic and mediastinal disorders			
Uncommon	cough	dyspnoea	dyspnoea, rhinitis
Very rare	interstitial lung disease		
Gastrointestinal disorder			
Common			altered bowel habits (including diarrhoea and constipation)
Uncommon	abdominal pain, diarrhoea, nausea	flatulence	
Rare	vomiting, gingival hypertrophy,	stomach discomfort	

	dyspepsia, dry mouth		
Very rare			pancreatitis, gastritis
Hepato-biliary disorders			
Rare		hepatic function abnormal, liver disorder	
Very rare			hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders			
Uncommon	pruritus	hyperhidrosis	alopecia, purpura, skin discolouration, hyperhidrosis
Rare	eczema, erythema, rash	angioedema (including fatal outcome), drug eruption, toxic skin eruption, urticaria	
Very rare			angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity
Not known			toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders			
Common			ankle swelling
Uncommon	arthralgia, muscle spasms (cramps in legs), myalgia		

Rare	back pain, pain in extremity (leg pain)	tendon pain (tendinitis like symptoms)	
Renal and urinary disorders			
Uncommon		renal impairment including acute renal failure	micturition disorder, pollakiuria
Rare	nocturia		
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	
Investigations			
Uncommon	hepatic enzymes increased	blood creatinine increased	weight increased, weight decreased
Rare	blood uric acid increased	blood creatine phosphokinase increased, haemoglobin decreased	

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. Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a

delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

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 10mg has been shown to reduce the absorption rate of amlodipine. Amlodipine is not dialysable and telmisartan is not removed from blood by haemofiltration and not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs) and calcium channel blockers.

ATC Code: C09DB04.

Telarb®-Plus combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor blocker, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Telarb®-Plus once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Mechanism of action:

Telmisartan: Telmisartan is an orally active and specific angiotensin II receptor (type 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 reactions. In humans, an 80mg 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.

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 non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

5.2. PHARMACOKINETICS PROPERTIES:

Pharmacokinetic of the fixed dose combination: The rate and extent of absorption of Telarb®-Plus are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Absorption: 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 ($AUC_{0-\infty}$) of telmisartan varies from approximately 6% (40mg dose) to approximately 19% (160mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food. 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.

Distribution: Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l. The volume of distribution of amlodipine is approximately 21 l/kg.

Biotransformation: Telmisartan is metabolized by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Amlodipine is extensively (approximatively 90 %) metabolized by the liver to inactive metabolites.

Elimination: Telmisartan is characterized by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in

females than in males, without relevant influence on efficacy. After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1% of dose. Total plasma clearance (CL_{tot}) is high (approximately 1,000ml/min) compared with hepatic blood flow (about 1,500ml/min). 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.

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. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40mg.

5.3. PRECLINICAL SAFETY DATA:

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10mg/kg of telmisartan and amlodipine were tested. Preclinical data available for the components of this fixed dose combination are reported below.

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 blockers, 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 blockers, 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 doses approximately 50 times greater than the maximum recommended dose 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 10mg amlodipine/kg/day (about 8 times* the maximum recommended human dose of 10mg/day on an mg/m^2 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, mutagenesis: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dose levels of 0.5, 1.25, and 2.5mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10mg on a mg/m^2 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Telarb®-Plus 40mg/5mg Tablet:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets
- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Pregelatinized Starch
- Maize Starch
- Apple Green Lake Color
- Silicon Dioxide Fumed

Telarb®-Plus 40mg/10mg Tablet:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets

- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Pregelatinized Starch
- Maize Starch
- Tartrazine Yellow Lake Color
- Silicon Dioxide Fumed

Telarb®-Plus 80mg/5mg Tablet:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets
- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Pregelatinized Starch
- Maize Starch
- Apple Green Lake Color
- Silicon Dioxide Fumed

Telarb®-Plus 80mg/10mg Tablet:

- Microcrystalline Cellulose
- Meglumine
- Crosscarmellose Sodium
- Crospovidone
- Sodium Starch Glycolate
- Sodium Hydroxide Pellets
- Magnesium Stearate
- Isopropyl Alcohol
- Purified Water
- Pregelatinized Starch
- Maize Starch
- Tartrazine Yellow Lake Color
- Silicon Dioxide Fumed

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

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

6.5. NATURE AND CONTENTS OF CONTAINER:

Telarb®-Plus 40mg/5mg Tablet: Alu/Alu blister packing, pack size is 14's.
Telarb®-Plus 40mg/10mg Tablet: Alu/Alu blister packing, pack size is 14's.
Telarb®-Plus 80mg/5mg Tablet: Alu/Alu blister packing, pack size is 14's.
Telarb®-Plus 80mg/10mg Tablet: Alu/Alu blister packing, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

The medicine 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.
Any unused product should be disposed of in accordance to local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Telarb®-Plus 40mg/5mg Tablet: USP Specs.
Telarb®-Plus 40mg/10mg Tablet: USP Specs.
Telarb®-Plus 80mg/5mg Tablet: USP Specs.
Telarb®-Plus 80mg/10mg Tablet: 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®-Plus 40mg/5mg Tablet: 100515
Telarb®-Plus 40mg/10mg Tablet: 100925
Telarb®-Plus 80mg/5mg Tablet: 100924
Telarb®-Plus 80mg/10mg Tablet: 100926

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Telarb®-Plus 40mg/5mg Tablet: 19th December, 2019

Telarb®-Plus 40mg/10mg Tablet: 19th December, 2019
Telarb®-Plus 80mg/5mg Tablet: 19th December, 2019
Telarb®-Plus 80mg/10mg Tablet: 19th December, 2019

10. DATE OF REVISION OF THE TEXT

ٹیل آرب®-پلس ٹیبلٹ

(ٹیلمیسارٹن + ایملو ڈیپین بیسیلیٹ)

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

ورنہ دوا خراب ہو جائیگی کے درمیان میں رکھیں۔