Telarb®-Plus Tablet

(Telmisartan + Amlodipine Besylate)

WARNING: FETAL TOXICITY: When pregnancy is detected, discontinue Telarb®-Plus as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

QUALITATIVE & 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

PHARMACEUTICAL FORM: Tablets

CLINICAL PARTICULARS: THERAPEUTIC INDICATIONS: **Telarb®-Plus** tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents. **Telarb®-Plus** tablets may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. Base the choice of **Telarb®-Plus** tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of **Telarb®-Plus** tablets. Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. Consider the patient's baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared with monotherapy when deciding whether to use **Telarb®-Plus** tablets as initial therapy. Individual blood pressure goals may vary based upon the patient's risk.

POSOLOGY AND METHOD OF ADMINISTRATION:

Posology: General Considerations: Telmisartan is an effective treatment of hypertension in once daily doses of 20 to 80mg while amlodipine is effective in doses of 2.5 to 10mg. Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of **Telarb®-Plus** tablets is 80mg/10mg once daily. The adverse reactions of telmisartan are uncommon and independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. Replacement Therapy: Patients receiving amlodipine and telmisartan from separate tablets may instead receive **Telarb®-Plus** tablets containing the same component doses once daily. When substituting for individual components, increase the dose of **Telarb®-Plus** if blood pressure control has not been satisfactory. Add-on Therapy for Patients with Hypertension Not Adequately Controlled on Antihypertensive Monotherapy: **Telarb®-Plus** tablets may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with telmisartan (or another angiotensin receptor blocker) alone. Patients treated with 10mg amlodipine who experience any dose-limiting adverse reactions such as edema, may be switched to **Telarb®-Plus** 40mg/5mg tablet once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response. Initial Therapy: A patient may be initiated on **Telarb®-Plus** tablets if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose of **Telarb®-Plus** is 40mg/5mg once daily. Patients requiring larger blood pressure reductions may be started on **Telarb®-Plus** 80mg/5mg once daily. Initial therapy with **Telarb®-Plus** is not recommended in patients •75 years old or with hepatic impairment. Correct imbalances of intravascular volume - or salt-depletion, before initiating therapy with **Telarb®-Plus** tablets. Renal Impairment: No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment. Hepatic Impairment: In most patients, initiate amlodipine therapy at 2.5mg. Titrate slowly in patients with hepatic impairment. Patients 75 Years of Age and Older: In most patients, initiate amlodipine therapy at 2.5mg. Titrate slowly in patients 75 years of age and older.

Method of administration: **Telarb®-Plus** tablets may be taken with or without food.

CONTRAINDICATIONS: **Telarb®-Plus** tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or amlodipine.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

FETAL TOXICITY: Pregnancy Category D: *Telmisartan:* Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue **Telarb®-Plus** as soon as possible. Hypotension:*Telmisartan*: In patients with an activated renin-angiotensin system, such as volume - or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with **Telarb®-Plus** tablets. Either correct this condition prior to administration of **Telarb®-Plus** tablets, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.*Amlodipine*: Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, observe patients with severe aortic stenosis closely when administering amlodipine, as one should with any vasodilator. Hyperkalemia:*Telmisartan:* Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk. Patients with Impaired Hepatic Function: *Telmisartan:* 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. Initiate telmisartan at low doses and titrate slowly in these patients. *Amlodipine:* Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5mg in patients with hepatic impairment. The lowest dose of **Telarb®-Plus** is 40mg/5mg; therefore, initial therapy with **Telarb®-Plus** tablets is not recommended in hepatically impaired patients. Renal Function Impairment: *Telmisartan:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors. Dual Blockade of the Renin-Angiotensin-Aldosterone System: *Telmisartan:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function. Concomitant use of telmisartan and ramipril is not recommended. Risk of Myocardial Infarction or Increased Angina: Amlodipine: Uncommonly, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated. Heart Failure: *Amlodipine*: Closely monitor patients with heart failure. Amlodipine (5 to 10mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure).

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Drug Interactions with **Telarb®-Plus** Tablets: The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered. No drug interaction studies have been conducted with **Telarb®-Plus** tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of **Telarb®-Plus** tablets.Drug Interactions with Telmisartan: *Digoxin:* When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under digitalization. *Lithium:* Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use. *Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):* In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors. *Ramipril and Ramiprilat:* Co-administration of telmisartan 80mg once daily and ramipril 10mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended. *Other Drugs:* Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19. Drug Interactions with Amlodipine: In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. Simvastatin: Co-administration of multiple doses of 10mg of amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20mg daily. The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, Maalox, sildenafil. Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

PREGNANCY AND LACTATION: Pregnancy: *Pregnancy Category D:* Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue **Telarb®-Plus** as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue **Telarb®-Plus**, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to **Telarb®-Plus** for hypotension, oliguria, and hyperkalemia. Breast-feeding:*Telmisartan:* It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of

210mm

120mm

the drug to the mother. *Amlodipine:* It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered. Paediatric Use: *Neonates with a history of in utero exposure to* **Telarb®-Plus**: If oliguria or hypotension occurs, direct attention toward 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. Safety and effectiveness of **Telarb®-Plus** in paediatric patients have not been established. Geriatric Use: **Telarb®-Plus** *Tablets:* No overall differences in efficacy or safety of **Telarb®-Plus** tablets were observed in this patient population. *Telmisartan:* Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and 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. Patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5mg to telmisartan. The lowest dose of **Telarb®-Plus** is 40mg/5mg; therefore, initial therapy with **Telarb®-Plus** tablets is not recommended in patients 75 years of age and older. Hepatic Insufficiency:Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5mg to telmisartan. The lowest dose of **Telarb®-Plus** is 40mg/5mg; therefore, initial therapy with **Telarb®-Plus** tablets is not recommended in hepatically impaired patients.

UNDESIRABLE EFFECTS: The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine. *Telmisartan:* The most frequently spontaneously reported events include headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (e.g. toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan. *Amlodipine:* Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine. Adverse reactions reported for amlodipine for indications other than hypertension may be found in the innovator prescribing information

OVERDOSE: *Telmisartan:* Limited data are available with regard to over dosage in humans. The most likely manifestations of over dosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis. *Amlodipine:* Single oral doses of amlodipine maleate equivalent to 40mg/kg and 100mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on mg/m² basis) caused a marked peripheral vasodilation and hypotension. Over dosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional over dosage of amlodipine is limited. Reports of intentional over dosage include a patient who ingested 250mg and was asymptomatic and was not hospitalized; another (120mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

PHARMACOLOGICAL PROPERTIES: MECHANISM OF ACTION: *Telmisartan*: 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, 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 AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not 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 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. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. 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.

PHARMACODYNAMIC PROPERTIES:Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs) and calcium channel blockers. ATC code: C09DB04

Telarb®-Plus tablets have been shown to be effective in lowering blood pressure. **Telarb®-Plus** is a combination of two drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, telmisartan. Both telmisartan and amlodipine, lower blood pressure by reducing peripheral resistance but through complementary mechanisms. *Telmisartan:* In normal volunteers, a dose of telmisartan 80mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid). *Amlodipine:* Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg). 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. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects. Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man.

PHARMACOKINETIC PROPERTIES: Absorption: The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately. After administering **Telarb®-Plus** 80mg/10mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and C_{max} for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and C_{max} were not altered.

Telmisartan: Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40mg tablet and about 20% after a 160mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Amlodipine: Peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Distribution:*Telmisartan:* Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and a1- 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 apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Metabolism and Elimination: *Telmisartan:* Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; 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. Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose. *Amlodipine:* Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

SHELF LIFE

See expiry on the pack

AVAILABILITY

Telarb®-Plus 40mg/5mg tablet in a pack of 14's

Telarb®-Plus 40mg/10mg tablet in a pack of 14's

Telarb®-Plus 80mg/5mg tablet in a pack 14's

Telarb®-Plus 80mg/10mg tablet in a pack of 14's

INSTRUCTIONS

Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

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

ٹیل آرب®-پلس ٹیبلٹ

(ٹیلمیسارٹن + ایملوڈیپین بیسیلیٹ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔

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