1.0 NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name: SUPLAVAT

1.2 Generic Name: Telmisartan & Amlodipine Tablets

1.3 Strength: 40 mg + 5 mg

1.4 Pharmaceutical Form: Tablets

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated Bilayered Tablet Contains:
Telmisartan USP 40 mg
Amlodipine Besylate USP eq. to
Amlodipine 5 mg
Colours: Lake of Ponceau 4R (In Amlodipine Besylate)

3.0 PHARMACEUTICAL FORM & DESCRIPTION

Oral Tablet

4.0 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of hypertension alone or with other antihypertensive agents to lower blood pressure.

4.2 DOSAGE AND ADMINISTRATION

Dosing Considerations

Telmisartan/Amlodipine should be taken with or without food the same way and at the same time, preferably in the morning, every day.

Recommended Dose

Telmisartan/Amlodipine should be taken once daily.

Replacement Therapy

Patients receiving Telmisartan and amlodipine from separate tablets can instead receive Telmisartan/Amlodipine containing the same component doses in one tablet once daily, e.g. to enhance convenience.

Renal impairment

No dosage adjustment is required for patients with renal impairment, including those on Haemodialysis.

Amlodipine and Telmisartan are not dialyzable. Amlodipine dosage requirement for patients with impaired renal function is 5 mg once daily. If required, increasing the dose should be done gradually and with caution.

Hepatic impairment

In patients with mild to moderate hepatic impairment Telmisartan/Amlodipine should be administered with caution. For Telmisartan the dosage should not exceed 40 mg once daily as hepatic impairment increases bioavailability. Amlodipine dosage requirement have not been established in patients with impaired hepatic function. When amlodipine is used in these patients, the dosage should be carefully and gradually adjusted depending on the patient's tolerance and response.

Elderly (> 65 years of age)

No dose adjustment is necessary for elderly patients. It should be recognized, however, that greater sensitivity in some older individuals cannot be ruled out.

Children and adolescents

Telmisartan/Amlodipine is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy

4.3 CONTRAINDICATIONS

Contraindicated in patients with known hypersensitivity to Telmisartan, Amlodipine. Do not Co - administer aliskiren with Telmisartan/Amlodipine in patients with diabetes.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

A case of rare but fatal angioedema had occurred in a patient who had been medicated for about 6 months with Telmisartan. The Autopsy Report described evidence of edema of the laryngeal mucosa, with terminal respiratory and circulatory failure. This is in the context of approximately 5.2 million patient-years exposure to Telmisartan annually. If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, Telmisartan/Amlodipine should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy should be administered promptly.

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. These patients are at risk of decreased coronary perfusion resulting from a cardiac output that is limited by a fixed cardiac vascular obstruction.

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. Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

Heart Failure:
In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV Heart Failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Intravascular Hypovolaemia:
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, Diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy. Such conditions should be corrected before the administration of Telmisartan/Amlodipine.

Peripheral Edema:
Peripheral edema is a recognised dose dependent side effect of amlodipine. In a single double blind, randomised, factorial clinical trial of eight weeks duration, edema was generally observed at a lower incidence in patients who received the Telmisartan/amlodipine combination than in those who received amlodipine alone.

Dual blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as the Telmisartan component of Telmisartan/Amlodipine, or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR< 60 ml/min/1.73m2). Therefore, the use of Telmisartan/Amlodipine in combination with Aliskiren containing drugs is contraindicated in these patients. Further, co-administration of ARBs, including the Telmisartan component of Telmisartan/Amlodipine, with other agents blocking the RAS, such as ACE inhibitors or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Concomitant Use with Strong Inhibitors of CYP 3A4:
Use of Telmisartan/Amlodipine with drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of amlodipine and associated serious adverse events. Such concomitant use should be avoided. An observational study demonstrated an increased risk of hospitalisation with acute kidney injury when amlodipine was used concomitantly with clarithromycin in elderly patients (>65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio.

Hepatic Impairment:
As the majority of Telmisartan is eliminated by biliary excretion, patients with cholestasis, biliary obstructive disorders or hepatic insufficiency have reduced clearance of Telmisartan leading to increased systemic exposure. Furthermore as with all calcium antagonists, Amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. 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.

Renal Impairment and Kidney Transplant:
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. Telmisartan and amlodipine are not dialyzable.

Blockade of the Renin-Angiotensin-Aldosterone System:
In patients whose renal function may depend on the activity of the renin-angiotensin aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, dual blockade or treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. Upon treatment in such cases, renal function should be closely monitored.

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/Amlodipine is not recommended.

Hyperkalaemia:
Drugs such as Telmisartan/Amlodipine that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of drugs that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or medicinal products that may increase potassium levels may lead to a greater risk of an increase in serum potassium and should therefore be co administered cautiously with Telmisartan.

Renal Impairment
The use of ARBs including the Telmisartan component of Telmisartan/Amlodipine or of ACEIs with aliskiren containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m2).

4.5 DRUG INTERACTIONS
Aliskiren: Do not co-administer aliskiren with Telmisartan/Amlodipine in patients with diabetes. Avoid use of aliskiren with Telmisartan/Amlodipine in patients with renal impairment (GFR <60 mL/min).
Digoxin:
When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed.
Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing Telmisartan for the purpose of keeping the digoxin level within the therapeutic range.
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:
In patients who are elderly, volume-depleted, or with compromised renal function, coadministration 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 Ramipril: Co-administration of Telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3-and 2.1-fold, respectively, and Cmax and AUC of ramipril 2.4-and 1.5-fold, respectively. In contrast, Cmax 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 ramipril in the presence of Telmisartan. Co-administration of Telmisartan and ramipril is not recommended.

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 amlodipine to 20 mg daily. The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid, sildenafil. Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following:

Atorvastatin, digoxin, warfarin. CYP3A4 Inhibitors Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors. CYP3A4 Inducers No information is available on the quantitative effects of CYP3A4 inducers (e.g., carbamazepine, phenobarbital, Phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort) on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

4.6 PREGNANCY AND LACTATION

Pregnancy

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 Telmisartan/Amlodipine 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 forest 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 Telmisartan/Amlodipine, 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 Telmisartan/Amlodipine for hypotension, oliguria, and hyperkalemia.

Lactation

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 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 UNDESIRABLE EFFECTS

Arrhythmia, Chest pain, Hypotension, Peripheral ischemia, Syncope, Tachycardia, Hypoesthesia, Neuropathy peripheral, Paraesthesia, Tremor, Anorexia, Constipation, Dyspepsia, Diarrhea, Asthenia, Back pain, Arthralgia, Muscle cramps, Insomnia, Nervousness, Depression, Dyspnea, Epistaxis, Angioedema, Erythema multiforme, pruritus, Rash, Abnormal vision, Conjunctivitis, Eye pain, Micturition frequency, Dry mouth, Sweating increased, Hyperglycaemia, Thirst, Leukopenia, Purpura

4.9 OVERDOSE

Symptoms

There is no experience of overdose with Telmisartan/Amlodipine. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects.

Telmisartan: Limited data are available with regard to Telmisartan Overdosage in humans. The most prominent manifestations of over dosage were hypotension and/or tachycardia; bradycardia also occurred.

Amlodipine: 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 may occur.

Therapy

If symptomatic hypotension should occur, supportive treatment should be instituted.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Telmisartan is an orally active non peptide angiotensin II antagonist that acts on the AT receptor subtype. 1 Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT receptor by binding reversibly 1 and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels. Studies also suggest that Telmisartan is a partial agonist of PPARy, which is an established target for antidiabetic drugs. This suggests that Telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPAR£^ activators. Amlodipine is a long-acting 1, 4-dihydropyridine calcium channel blocker. Amlodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the of calcium ions through L-type calcium channels.

Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplifications is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and results in vasodilation. The vasodilatory effects of amlodipine result in an overall decrease in blood pressure. Amlodipine is a long-acting CCB that may be used to treat mild to moderate essential hypertension and exertion-related angina (chronic stable angina). Another possible mechanism is that amlodipine inhibits vascular smooth muscle carbonic anhydrase I activity causing cellular pH increases which may be involved in regulating intracellular calcium influx through calcium channels.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Telmisartan: Following oral administration, Telmisartan is well absorbed, with a mean absolute bioavailability of about 50%. Mean peak concentrations of Telmisartan are reached in 0.5-1 hour after dosing.

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution

Telmisartan: Telmisartan is >99.5% bound to plasma protein, mainly albumin and alpha1- acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with therapeutic doses. The volume of distribution for Telmisartan is approximately 500 Liters, indicating additional tissue binding sites.

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

Metabolism

Telmisartan: Telmisartan is metabolized by conjugation with glucuronic acid to form an acylglucuronide of Telmisartan. This glucuronide is the only metabolite which has been identified in human plasma and urine.

Following both oral dosing and intravenous administration of radiolabeled Telmisartan, the parent compound represented approximately 85% and the glucuronide approximately 11% of total radioactivity in plasma.

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

Excretion

Telmisartan: Total plasma clearance of Telmisartan is >800 mL/min. Half-life and total clearance appear to be independent of dose. Biliary excretion is the main route of elimination of Telmisartan and its metabolite. Following intravenous and oral administration of C14 labelled Telmisartan 0.91% and 0.49% of administered dose were found in the urine as glucuronide, respectively.

Amlodipine: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. 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.

5.3 PRECLINICAL SAFETY DATA

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Starch BP
Microcrystalline Cellulose BP
Di- basic calcium phosphate (calcium Hydrogen) BP
Polyvinyl Pyrrolidone (PVPK 30) BP
Purified Water BP
Magnesium Stearate BP
Sodium Starch Glycolate Grade TYPE-A BP
Purified Talcum B
Croscarmellose Sodium USNF
Microcrystalline Cellulose BP
Sodium Starch Glycolate (Type-A) Grade BP
Col. Ponceau 4R Lake
Polyvinyl Pyrrolidone (PVPK 30) BP
Isopropyl Alcohol (IPA) BP

6.2 INCOMPATIBILITIES

No effect noted to date.

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light & moisture

6.5 NATURE AND CONTENTS OF CONTAINER

The finished product Telmisartan & amlodipine tablets is supplied in a strip. The pack size is 10 x10 Tablets packed in a Strip.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements.

7. MARKETING AUTHORIZATION HOLDER:

Superior Pharmaceuticals Ltd
9B Robinson Gbagi St,
Ajao Estate, Lagos, Nigeria

8. NAME AND ADDRESS OF THE MANUFACTURER

AKUMS DRUGS & PHARMACEUTICALS LTD. Plant I,
Plot No. 19, 20 & 21, Sector 6A IIE, SIDCUL, Ranipur,
District: Haridwar, Uttarakhand INDIA.