PROFESSIONAL INFORMATION FOR STYTEM 40/5, 40/10, 80/5, 80/10

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

STYTEM 40/5 tablets
STYTEM 40/10 tablets
STYTEM 80/5 tablets
STYTEM 80/10 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STYTEM 40/5 mg tablets: Each tablet contains 40 mg telmisartan and 5 mg amlodipine base (as besilate salt). Contains sugar (mannitol) 169,94 mg per tablet.

STYTEM 40/10 mg tablets: Each tablet contains 40 mg telmisartan and 10 mg amlodipine base (as besilate salt). Contains sugar (mannitol) 169,94 mg per tablet.

STYTEM 80/5 tablets: Each tablet contains 80 mg telmisartan and 5 mg amlodipine base (as besilate salt). Contains sugar (mannitol) 339,88 mg per tablet.

STYTEM 80/10 tablets: Each tablet contains 80 mg telmisartan and 10 mg amlodipine base (as besilate salt). Contains sugar (mannitol) 339,88 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

STYTEM 40/5: Oval shaped biconvex, bilayer, uncoated tablets with one white to off- white colour layer and one blue colour mottled layer debossed with “L389”.

STYTEM 40/10: Oval shaped biconvex, bilayer, uncoated tablets with one white to off- white colour layer and one blue colour mottled layer debossed with “L390”.

STYTEM 80/5: Oval shaped biconvex, bilayer, uncoated tablets with one white to off-white colour layer and one blue colour mottled layer debossed with “L391”.

STYTEM 80/10: Oval shaped biconvex, bilayer, uncoated tablets with one white to off- white colour layer and one blue colour mottled layer debossed with “L388”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy:
Treatment of essential hypertension in patients who have been stabilised on the two component medicines used at the same dose.

Add on therapy:
STYTEM is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

4.2 Posology and method of administration

Posology:
STYTEM should be taken once daily.

Replacement Therapy:
Patients taking telmisartan and amlodipine as separate tablets can instead take STYTEM containing the same component doses in one tablet once daily.

Add on therapy:
STYTEM may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone.

The usual starting dose of STYTEM is 40/5 mg once daily.

If additional blood pressure lowering is needed after at least 2 weeks of therapy, the dose may be titrated up to a maximum of 80/10 mg once daily.

Special populations
Renal impairment:
No dosage adjustment is required for patients with mild to moderate renal impairment (see section 4.4).

Amlodipine and telmisartan are not dialysable.

Hepatic impairment:
In patients with mild to moderate hepatic impairment STYTEM should be administered with caution. For telmisartan, the dose should not exceed 40/5 mg or 40/10 mg once daily.

Elderly:
No dose adjustment is necessary for elderly patients.

Children and adolescents:
STYTEM is not recommended for use in patients aged below 18 years.

Method of administration:
Oral use.

STYTEM may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to telmisartan, amlodipine or any of the other excipient of STYTEM listed in section 6.1.
- Hypersensitivity to dihydropyridine derivatives.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- The concomitant use of STYTEM with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).
- Lithium therapy: concomitant administration with STYTEM may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Biliary obstructive disorders.
- Severe hepatic impairment.
- Cardiogenic shock.
- Concomitant use of fluoroquinolones with Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Pregnancy:

Should a woman become pregnant while receiving STYTEM, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. (See section 4.6).

STYTEM should not be initiated during pregnancy (see section 4.6).

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 STYTEM should be stopped immediately, and if appropriate, alternative therapy should be started (see section 4.6).

Hepatic impairment:
Telmisartan (ingredient of STYTEM) is mostly eliminated in the bile.

Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Amlodipine's half-life life is prolonged in patients with impaired liver functions and dosage recommendations have not been established.

STYTEM should therefore be used with caution in patients with mild to moderate impairment of liver function, and should not be used in patients with severe liver impairment (see section 4.3).

Renal impairment and kidney transplant:
When STYTEM 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 STYTEM in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

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 medicines that affect the renin-angiotensin-aldosterone system (RAAS) (see section 4.3).

Intravascular hypovolaemia:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g., vigorous diuretic therapy, dietary salt restrictions, diarrhoea or vomiting. Such conditions should be corrected before the administration of STYTEM.

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 may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of STYTEM and aliskiren is therefore contraindicated (see section 4.3).

STYTEM should not be used concomitantly with aliskiren (see section 4.3).

Other conditions with stimulation of the renin-angiotensin- aldosterone systems:
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 STYTEM, that affects this system, has been associated with acute hypotension, hyperuraemia, oliguria or rarely acute renal failure.

Concomitant use of fluoroquinolones:
Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzymes (ACE) inhibitors/Angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of STYTEM is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy:
STYTEM is contraindicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy.

Unstable angina pectoris, acute myocardial infarction:
There are no data to support the use of STYTEM in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure:
The use of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology is associated with pulmonary oedema.

Hyperkalaemia:
During treatment with STYTEM, hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicines that affect the renin-angiotensin-system, concomitant use with concomitant use with potassium supplements, salt substitutes containing potassium or other medicines that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with STYTEM.

Diabetes mellitus:
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes Mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed.

Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g., exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with STYTEM.

Other:
Excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease may result in a myocardial infarction or stroke.

Mannitol:
STYTEM tablets contain mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction
There are no interactions between the two components (telmisartan and amlodipine) of the fixed dose combination.

Interactions common to the combination:
No interaction studies have been performed with STYTEM and other medicines.

Interactions to be taken into account with concomitant use:
Other antihypertensive medicines:
The blood pressure lowering effect of STYTEM can be increased by concomitant use of other antihypertensive medicines.

Medicines with blood pressure lowering potential:
Based on their pharmacological properties it can be expected that the following medicines may potentiate the hypotensive effects of STYTEM e.g. baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route):
Concomitant use with corticosteroids causes a reduction of the antihypertensive effect.

Interactions linked to the telmisartan component of STYTEM:
Telmisartan may increase the hypotensive effect of other antihypertensive medicines. Other interactions of clinical significance have not been identified.

Co-administration of telmisartan does not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin in a 20 % increase in median plasma digoxin trough concentration has been observed (39 % in a single case); monitoring of plasma digoxin levels should be considered.

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.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Increased serum levels have also been reported with telmisartan.

Treatment with NSAIDs (i.e., aspirin at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the renin-angiotensin-system like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive medicines like telmisartan by inhibition of vasodilating prostaglandins occurs during combined treatment with NSAIDs.

Dual blockade of the RAAS with ARB's ACE inhibitors or aliskiren:
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Interactions linked to the amlodipine component of STYTEM:
Concomitant use requiring caution:
CYP3A4 inhibitors:
Diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50 % and the effect of amlodipine is increased).

The possibility that more potent inhibitors of CYP3A4 (i.e., ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant medicines [e.g., carbamazepine, phenobarbitone, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum):
Co-administration may lead to reduced plasma concentrations of amlodipine.

Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

Concomitant use to be taken into account:
Others:
In monotherapy, amlodipine is safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory medicines, antibiotics and oral hypoglycaemic combination. When amlodipine and sildenafil were used in combination, each medicine independently exerts its own blood pressure lowering effect.

Additional information:
Concomitant administration of 240 mL of grapefruit juice with a single oral dose of 10 mg amlodipine does not show a significant effect on the pharmacokinetic properties of amlodipine.

Co-administration of amlodipine with cimetidine has no significant effect on the pharmacokinetics of amlodipine.

Co-administration of amlodipine with atorvastatin, digoxin, warfarin or ciclosporin has no significant effect on the pharmacokinetics or pharmacodynamics of these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established (see section 4.3).

When pregnancy is planned or confirmed, STYTEM should be discontinued (see section 4.3).

Medicines affecting the renin-angiotensin system, such as STYTEM, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. Should exposure to STYTEM have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken STYTEM should be closely observed for hypotension.

Women of Childbearing potential:

Women of childbearing age should ensure adequate contraception.

Lactation:

Safety in lactation has not been established (see section 4.3).

It is not known whether telmisartan and/or amlodipine (as in STYTEM) are excreted in human milk. Excretion of telmisartan in breast milk is shown in animal studies. Because of the potential adverse reactions in breastfed infants,

STYTEM should not be used by breast feeding mothers.

Fertility:

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

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as syncope (fainting), somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a vehicle or operating machinery. If patients experience these adverse effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

a) Summary of adverse effects

The most frequent adverse reactions include dizziness and peripheral oedema.

Serious syncope may occur less frequently.

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

Tabulated summary of adverse effects

Fixed dose combination (STYTEM):

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Less frequent	Cystitis
Psychiatric disorders	Less frequent	Depression, anxiety, insomnia
Nervous system disorders	Frequent Less frequent	Dizziness Somnolence,migraine, headache, paraesthesia, syncope (fainting), peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders	Less frequent	Vertigo

Cardiac disorders	Less frequent	Bradycardia, palpitation
Vascular disorders	Less frequent	Hypotension, orthostatic hypotension, flushing
Respiratory, thoracic and mediastinal disorders	Less frequent	Cough
Gastro-intestinal disorders	Less frequent	Abdominal pain, diarrhoea, nausea, vomiting, gingival, hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, eczema, erythema, rash
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, muscle spasms, myalgia, back pain, pain in extremity
Renal and urinary disorders	Less frequent	Nocturia
Reproductive system and breast disorders	Less frequent	Erectile dysfunction
General disorders	Frequent Less frequent	Oedema, peripheral Asthenia, chest pain, fatigue, oedema, malaise
Investigations	Less frequent	Hepatic enzymes increased, blood uric acid increased

The following side effects are expected based on experience with telmisartan monotherapy, but the frequencies are not determined:

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Frequency unknown	Sepsis including fatal outcome, urinary tract infections, upper respiratory tract infections
Blood and the lymphatic system disorders	Frequency unknown	Anaemia, eosinophilia, thrombocytopenia
Immune system disorders	Frequency unknown	Angioedema, anaphylactic reaction, hypersensitivity
Metabolism and nutritional disorders	Frequency unknown	Hyperkalaemia
Eye disorders	Frequency unknown	Visual disturbance
Cardiac disorders	Frequency unknown	Tachycardia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea
Gastro-intestinal disorders	Frequency unknown	Flatulence, stomach discomfort
Hepato-biliary disorders	Frequency unknown	Hepatic function abnormal, liver disorder
Skin and subcutaneous tissue disorders	Frequency unknown	Hyperhidrosis, urticaria, medicine eruption, toxic skin eruption
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Tendon pain
Renal and urinary disorders	Frequency unknown	Renal impairment
General disorders	Frequency unknown	Influenza-like illness

Investigations	Frequency unknown	Haemoglobin decreased, blood creatinine increased, blood creatinine phosphokinase (CPK) increased.

The following side effects are expected based on experience with amlodipine monotherapy, but the frequencies are not determined:

System Organ Class	Frequency	Adverse reaction
Blood and the lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity
Metabolism and nutritional disorders	Frequency unknown	Hyperglycaemia
Psychiatric disorders	Frequency unknown	Mood change
Eye disorders	Frequency unknown	Visual impairment
Ear and labyrinth disorders	Frequency unknown	Tinnitus
Cardiac disorders	Frequency unknown	Myocardial infarction, dysrhythmia, ventricular tachycardia, atrial fibrillation
Vascular disorders	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea, rhinitis
Gastro-intestinal disorders	Frequency unknown	Change of bowel habit, pancreatitis, gastritis
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)
Skin and subcutaneous tissue disorders	Frequency unknown	Hyperhidrosis, urticaria, alopecia, purpura, skin discolouration, erythema multiforme
Renal and urinary disorders	Frequency unknown	Micturition disorder, pollakiuria
Reproductive and breastfeeding disorders	Frequency unknown	Gynaecomastia
General disorders	Frequency unknown	Pain, weight increased, weight decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms
Signs and symptoms of overdosage are expected to be in line with exaggerated pharmacological effects.

The most prominent manifestations of telmisartan overdosage were hypotension, tachycardia, bradycardia might also occur.

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.

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.

Therapy:
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

A 7.1.3 Vascular medicine – other hypotensives.

STYTEM combines two antihypertensive medicines with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine. The combination of these medicines has an additive antihypertensive effect.

Mechanism of action

Telmisartan:
Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II 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. The binding is long lasting.

Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan monotherapy. Telmisartan monotherapy does not inhibit human plasma renin or block ion channels.

In man, an 80 mg dose of telmisartan monotherapy almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and is still measurable up to 48 hours.

After administration of the first dose of telmisartan monotherapy, onset of antihypertensive activity occurs within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.

There is an apparent trend to a dose relationship with regard to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent. In patients with hypertension telmisartan monotherapy reduces both systolic and diastolic blood pressure without affecting pulse rate.

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.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine results in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without a change in filtration fraction or proteinuria.

STYTEM:
Treatment with each combination dose of STYTEM results in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy.

The antihypertensive effect of STYTEM is similar irrespective of age and gender and is similar in patients with and without diabetes.

5.2 Pharmacokinetic properties
Pharmacokinetics of the fixed dose combination (Telmisartan and Amlodipine):

The rate and extent of absorption of STYTEM are similar to the bioavailability of Telmisartan and Amlodipine when administered as individual tablets.

Pharmacokinetics of the single components:
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When the fixed dose combination is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan was approximately 25 % at a dose of 80/10 mg. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

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.

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_{ss}) is approximately 500 L. 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.

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

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

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 hour. The maximum plasma concentration (Cmax) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is < 2 % of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min) compared with hepatic blood flow (about 1 500 mL/min).

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 percent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Paediatric patients (age below 18 years):
No pharmacokinetic data are available in the paediatric population.

Gender effects:
Gender differences in plasma concentration of telmisartan were observed, C_{max} and AUC being approximately 3 and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.

Elderly patients:
The pharmacokinetics of telmisartan do not differ between younger and elderly patients. Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life.

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

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

Patients with hepatic impairment:
Pharmacokinetics properties in patients with hepatic impairment shows an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40 – 60 % in AUC.

5.3 Preclinical safety data
Not applicable.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Blue colourant
Corn starch
Crospovidone
Iron oxide black
Magnesium stearate
Mannitol
Meglumine
Microcrystalline cellulose
Povidone-K
Sodium stearyl fumarate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at or below 30 °C.
Store in the original package.
Protect from light and moisture.

6.5 Nature and contents of container
30 Tablets in aluminium blister strips of 10 tablets per strip with 3 strips packed in a unit carton.
Pack size: 30 tablets

6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION
Forrester Pharma (Pty) Ltd
2 Waterford Mews
Waterford Place
Century City
Cape Town
7441
South Africa

8. REGISTRATION NUMBERS
STYTEM 40/5: 50/7.1.3/0509
STYTEM 40/10: 50/7.1.3/0510
STYTEM 80/5: 50/7.1.3/0511
STYTEM 80/10: 50/7.1.3/0512

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 11 February 2020