Teva Pharmaceuticals (Pty) Ltd.	**Product:** **TENSITEV 40/5; 40/10; 80/5; 80/10** **Dosage Form:** Tablets **Strength:** Each tablet contains 40 mg telmisartan and 5 mg or 10 mg amlodipine (as besilate), respectively Each tablet contains 80 mg telmisartan and 5 mg or 10 mg amlodipine (as besilate), respectively
Reg. No.: 57/7.1.3/0340 57/7.1.3/0341 57/7.1.3/0342 57/7.1.3/0343	

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

TENSITEV 40/5 (tablets)

TENSITEV 40/10 (tablets)

TENSITEV 80/5 (tablets)

TENSITEV 80/10 (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TENSITEV 40/5: Each tablet contains 40 mg telmisartan and amlodipine besilate equivalent to 5 mg amlodipine.

TENSITEV 40/10: Each tablet contains 40 mg telmisartan and amlodipine besilate equivalent to 10 mg amlodipine.

TENSITEV 80/5: Each tablet contains 80 mg telmisartan and amlodipine besilate equivalent to 5 mg amlodipine.

TENSITEV 80/10: Each tablet contains 80 mg telmisartan and amlodipine besilate equivalent to 10 mg amlodipine.

TENSITEV contains sugar (mannitol: 98,505 mg, 98,36 mg (TENSITEV 40/5 & 40/10); 197,01 mg and 196,72 mg (TENSITEV 80/5 & 80/10) per tablet respectively.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Tablets.

TENSITEV 40/5: bilayer tablets, white to off-white on one side and pink on the other side, acceptable slight speckles on the pink side, oblong, biconvex.

TENSITEV 40/10: bilayer tablets, white to off-white on one side and yellow on the other side, acceptable slight speckles on the yellow side, oblong, biconvex.

TENSITEV 80/5: bilayer tablets, white to off-white on one side and pink on the other side, acceptable slight speckles on the pink side, oblong, biconvex.

TENSITEV 80/10: bilayer tablets, white to off-white on one side and yellow on the other side, acceptable slight speckles on the yellow side, oblong, biconvex.

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:

TENSITEV is indicated in patients whose blood pressure is not adequately controlled on amlodipine monotherapy.

4.2 Posology and method of administration:

TENSITEV should be taken once daily.

Replacement Therapy:

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

Add on therapy:

TENSITEV may be administered in patients whose blood pressure is not adequately controlled with amlodipine alone.

The usual starting dose of TENSITEV 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 TENSITEV should be administered with caution. For telmisartan the dose should not exceed 40 mg once daily (i.e. TENSITEV 40/5 mg or 40/10 mg).

Elderly:

No dose adjustment is necessary for elderly patients. Normal amlodipine dosage regimens are recommended in the elderly but increase of dosage should take place with care (see **sections 4.4** and **5.2**).

Paediatric population:

Children and adolescents:

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

Method of administration:

Tablet for oral administration.

TENSITEV may be taken with or without food.

4.3 Contraindications:

- Hypersensitivity to telmisartan, amlodipine, dihydropyridine derivatives, or to any of the ingredients of TENSITEV listed in **section 6.1**
- 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 (creatinine clearance less than 30 mL/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **section 4.5**)
- Porphyria
- Lithium therapy: Concomitant administration with TENSITEV may lead to toxic blood concentrations of lithium (see **section 4.5**)
- Pregnancy and lactation (see **section 4.6**)
- The concomitant use of TENSITEV with aliskiren-containing products is contraindicated (see **sections 4.4** and **4.5**)
- Biliary obstructive disorders
- Severe hepatic impairment
- Severe hypotension
- Shock (including cardiogenic shock)
- Haemodynamically unstable heart failure after acute myocardial infarction
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin blockers such as TENSITEV is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.
- Obstruction of the outflow tract of the left ventricle (e.g high grade aortic stenosis).

4.4 Special warnings and precautions for use:

Should a woman become pregnant while receiving TENSITEV, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and **4.6).**

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) 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 TENSITEV and aliskiren is therefore contraindicated (see **section 4.3**).

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

Pregnancy:

TENSITEV should not be initiated during pregnancy (see **section 4.3**).

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

Hepatic impairment:

Telmisartan as contained in TENSITEV 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 as contained in TENSITEV is prolonged in patients with impaired liver function and dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end

of the dosing range (i.e. TENSITEV 40/5 or 80/5) and caution should be used, both on initial treatment and when increasing the dose. TENSITEV 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**).

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 (see **section 4.3**).

Renal impairment and kidney transplant:

When TENSITEV 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 TENSITEV in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia:

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

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 TENSITEV, that affects this system, has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers such as TENSITEV 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 ACE inhibitors/angiotensin receptor blockers (i.e., TENSITEV) 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 TENSITEV is not recommended.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy:

TENSITEV 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 TENSITEV in unstable angina pectoris and during or within one month of a myocardial infarction.

Patients with cardiac failure:

In a long-term placebo-controlled study of amlodipine in patients with New York Heart Association (NYHA) class III and IV heart failure of non-ischaemic aetiology; amlodipine as contained in TENSITEV, was associated with increased reports of pulmonary oedema. Therefore, patients with heart failure should be treated with caution.

Calcium channel blockers, including amlodipine as contained in TENSITEV, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hyperkalaemia:

During treatment with TENSITEV 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 potassium-sparing diuretics, 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 TENSITEV.

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 medicines such as

ARBs or ACE-inhibitors such as TENSITEV. 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 TENSITEV.

Elderly patients:

The increase of the amlodipine dose as contained in TENSITEV should take place with care in the elderly patients (see **sections 4.2** and **5.2**).

Other:

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

Sodium:

Each tablet contains less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

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

Interactions linked to the combination:

No interaction studies have been performed with TENSITEV and other medicines.

Other antihypertensive medicines:

The blood pressure lowering effect of TENSITEV 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 TENSITEV: e.g., baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route):

Reduction of the antihypertensive effect.

Interactions linked to the telmisartan component of TENSITEV:

Concomitant use not recommended:

Potassium sparing diuretics or potassium supplements:

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

Lithium:

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

Dual blockage of the RAAS with ARBs, 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**).

Concomitant use requiring caution:

Non-steroidal anti-inflammatory medicinal products:

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. Medicines 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.

Ramipril:

In one study 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.

Fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers such as TENSITEV, may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see **section 4.3**).

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 the amlodipine component of TENSITEV:

Concomitant use not recommended:

Grapefruit and grapefruit juice:

Administration of TENSITEV 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 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 pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers:

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

Dantrolene (infusion):

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

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 TENSITEV 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 TENSITEV, 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, TENSITEV may increase exposure of mTOR inhibitors.

Simvastatin:

Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Additional information:

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation:

TENSITEV should not be used during pregnancy and lactation (see **section 4.3**).

Effects related to the mono components are described below.

Women of Childbearing Potential:

Women of childbearing age should ensure effective contraception.

Pregnancy:

Telmisartan:

Safety in pregnancy and lactation has not been established (see **section 4.3**). When pregnancy is planned or confirmed TENSITEV should be discontinued.

Medicines affecting the renin-angiotensin system, such as TENSITEV, 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 TENSITEV have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

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

Amlodipine:

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding:

TENSITEV is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. 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 to 7 %, with a maximum of 15 %.

The effect of amlodipine on infants is unknown. Because of the potential adverse reactions in breastfed infants, TENSITEV should not be used by breastfeeding mothers (see **section 4.3**).

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 (see **section 4.8**). 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:

Summary of the safety profile:

The most frequent adverse reactions include dizziness and peripheral oedema. Serious syncope may occur less frequently.

Tabulated summary of adverse reactions:

The following side effects derived from the use of the TENSITEV (telmisartan and amlodipine combination) or the use of the monocomponents (telmisartan or amlodipine) in clinical trials or from post-marketing experience are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms.

MedDRA SOC	**Fixed Dose Combination**	**Telmisartan monotherapy**	**Amlodipine monotherapy**
Infections and infestations:			
Sepsis (including fatal outcome)	-	Less frequent	-
Upper respiratory tract infection	-	Less frequent	-
Urinary tract infection	-	Less frequent	-
Cystitis	Less frequent	Less frequent	-
Blood and the lymphatic system disorders:			
Leukopenia	-	-	Less frequent
Thrombocyto-penia	-	Less frequent	Less frequent

Anaemia	-	Less frequent	-
Eosinophilia	-	Less frequent	-
Immune system disorders:			
Anaphylactic reaction	-	Less frequent	-
Hypersensitivity	-	Less frequent	Less frequent
Angioedema (with fatal outcome)	-	Less frequent	Less frequent
Metabolism and nutrition disorders:			
Hyperkalaemia	-	Less frequent	-
Hypoglycaemia (in diabetic patients)	-	Less frequent	-
Hyperglycaemia	-	-	Less frequent
Psychiatric disorders:			
Depression	Less frequent	Less frequent	Less frequent
Anxiety	Less frequent	Less frequent	Less frequent
Confusional state	-	-	Less frequent
Insomnia	Less frequent	Less frequent	Less frequent
Altered mood	-	-	Less frequent
Nervous system disorders:			

Syncope (fainting)	Less frequent	Less frequent	Less frequent
Somnolence	Less frequent	-	Frequent
Dizziness	Frequent	-	Frequent
Extrapyramidal disorder	-	-	Frequency unknown
Hypertonia	-	-	Less frequent
Migraine	Less frequent	-	-
Headache	Less frequent	-	Frequent
Neuropathy peripheral	Less frequent	-	Less frequent
Paraesthesia	Less frequent	-	Less frequent
Hypoaesthesia	Less frequent	-	Less frequent
Dysgeusia	Less frequent	-	Less frequent
Tremor	Less frequent	-	Less frequent
Eye disorders:			
Visual impairment	-	Less frequent	Frequent
Diplopia	-	-	Frequent
Ear and labyrinth disorders:			
Vertigo	Less frequent	Less frequent	-
Tinnitus	-	-	Less frequent
Cardiac disorders:			

Myocardial infarction	-	-	Less frequent
Ventricular tachycardia	-	-	Less frequent
Dysrhythmia	-	-	Less frequent
Atrial fibrillation	-	-	Less frequent
Bradycardia	Less frequent	Less frequent	Less frequent
Tachycardia	-	Less frequent	-
Palpitations	Less frequent	-	Frequent
Vascular disorders:			
Hypotension	Less frequent	Less frequent	Less frequent
Orthostatic hypotension	Less frequent	Less frequent	-
Flushing	Less frequent	-	Frequent
Vasculitis	-	-	Less frequent
Respiratory, thoracic and mediastinal disorders:			
Dyspnoea	-	Less frequent	Frequent
Cough	Less frequent	-	Less frequent
Rhinitis	-	-	Less frequent
Gastrointestinal disorders:			
Pancreatitis	-	-	Less frequent
Gastritis	-	-	Less frequent
Abdominal pain	Less frequent	Less frequent	Frequent

Diarrhoea	Less frequent	Less frequent	Frequent
Vomiting	Less frequent	Less frequent	Less frequent
Gingival hypertrophy	Less frequent	-	Less frequent
Dyspepsia	Less frequent	Less frequent	Frequent
Constipation	-	-	Frequent
Nausea	Less frequent	-	Frequent
Dry mouth	Less frequent	Less frequent	Less frequent
Flatulence	-	Less frequent	-
Abdominal discomfort	-	Less frequent	-
Change of bowel habit	-	-	Frequent
Hepato-biliary disorders:			
Hepatitis	-	-	Less frequent
Jaundice	-	-	Less frequent
Hepatic function abnormal/liver disorder	-	Less frequent	-
Hepatic enzyme increased (mostly consistent with cholestasis)	-	-	Less frequent

Skin and subcutaneous tissue disorders:			
Toxic epidermal necrolysis	-	-	Frequency unknown
Stevens-Johnson syndrome	-	-	Less frequent
Erythema multiforme	-	-	Less frequent
Dermatitis exfoliative	-	-	Less frequent
Drug eruption	-	Less frequent	-
Toxic skin eruption	-	Less frequent	-
Photosensitivity reaction	-	-	Less frequent
Urticaria	-	Less frequent	Less frequent
Eczema	Less frequent	Less frequent	-
Erythema	Less frequent	Less frequent	-
Rash	Less frequent	Less frequent	Less frequent
Pruritus	Less frequent	Less frequent	Less frequent
Alopecia	-	-	Less frequent
Purpura	-	-	Less frequent
Skin discolouration	-	-	Less frequent

Hyperhidrosis	-	Less frequent	Less frequent
Musculoskeletal, connective tissue and bone disorders:			
Arthralgia	Less frequent	Less frequent	Less frequent
Back pain	Less frequent	Less frequent	Less frequent
Pain in extremity (leg pain)	Less frequent	Less frequent	-
Tendon pain (tendonitis like symptoms)	-	Less frequent	-
Joint swelling	-	-	Frequent
Muscle spasms (cramps in legs)	Less frequent	Less frequent	Frequent
Myalgia	Less frequent	Less frequent	Less frequent
Renal and urinary disorders:			
Renal impairment (including acute renal injury)	-	Less frequent	-
Nocturia	Less frequent	-	Less frequent
Micturition disorder	-	-	Less frequent
Pollakiuria	-	-	Less frequent
Reproductive system and breast disorders:			

Erectile dysfunction	Less frequent	-	Less frequent
Gynaecomastia	-	-	Less frequent
General disorders and administration site conditions:			
Chest pain	Less frequent	Less frequent	Less frequent
Pain	-	-	Less frequent
Oedema	Less frequent	-	Frequent
Oedema peripheral	Frequent	-	-
Asthenia (weakness)	Less frequent	Less frequent	Frequent
Fatigue	Less frequent	-	Frequent
Malaise	Less frequent	-	Less frequent
Influenza like illness	-	Less frequent	-
Investigations:			
Increased hepatic enzyme	Less frequent	Less frequent	-
Increased blood creatinine	-	Less frequent	-
Increased blood creatine phosphokinase	-	Less frequent	-

Decreased haemoglobin	-	Less frequent	-
Increased blood uric acid	Less frequent	Less frequent	-
Increased weight	-	-	Less frequent
Decreased weight	-	-	Less frequent

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

4.9 Overdose:

Symptoms:

There is no experience of overdose with TENSITEV. Signs and symptoms of overdose 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 to 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.

In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

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 medicines – other hypotensives

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

TENSITEV combines two antihypertensive compounds with different mechanisms of action: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect.

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 AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan 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 resulted 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.

Combination of substances:

Treatment with each combination dose of TENSITEV resulted 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 was attained within 2 weeks after initiation of therapy.

The antihypertensive effect of the combination of telmisartan and amlodipine was similar irrespective of age and gender and was similar in patients with and without diabetes.

The combination of telmisartan and amlodipine has not been studied in any patient population other than hypertension.

5.2 Pharmacokinetic properties:

Pharmacokinetics of the Fixed Dose Combination:

The rate and extent of absorption of the fixed dose combination are similar to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Pharmacokinetics of the single components:

Absorption:

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 to 12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected 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_{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.

Biotransformation:

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.

Elimination:

Telmisartan is characterised by bi-exponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours. The maximum plasma concentration (C_{max}) 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 l 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 to 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 concentrations 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:

Pharmacokinetic studies in patients with hepatic impairment showed 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 to 60 % in AUC.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Telmisartan layer:

Cellulose, microcrystalline

Crospovidone

Iron oxide red (E172) (40/5 and 80/5 strength)

Iron oxide yellow (E172) (40/10 and 80/10 strength)

Magnesium stearate

Mannitol

Meglumine

Povidone K25

Sodium hydroxide

Amlodipine layer:

Cellulose, microcrystalline

Magnesium stearate

Silica, colloidal anhydrous

Starch, pregelatinized (maize)

Starch, maize

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store at or below 25 ˚C. Store in the original package to protect from light.

6.5 Nature and contents of container:

TENSITEV tablets are packed in Aluminium/OPA/Aluminium/PVC blister packs.

The blisters are placed together with a patient information leaflet into cardboard boxes with imprinted label text.

Pack size: 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

2090

South Africa

8. REGISTRATION NUMBER(S):

57/7.1.3/0340

57/7.1.3/0341

57/7.1.3/0342

57/7.1.3/0343

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

24 June 2025

10. DATE OF REVISION OF THE TEXT:

Teva Pharmaceuticals (Pty) Ltd.	**Product:** **TENSITEV 40/5; 40/10; 80/5; 80/10** **Dosage Form:** Tablets **Strength:** Each tablet contains 40 mg telmisartan and 5 mg or 10 mg amlodipine (as besilate), respectively Each tablet contains 80 mg telmisartan and 5 mg or 10 mg amlodipine (as besilate), respectively
Reg. No.: 57/7.1.3/0340 57/7.1.3/0341 57/7.1.3/0342 57/7.1.3/0343	