PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

TRI-PLEN 2,5 mg/2,5 mg film-coated tablets

TRI-PLEN FORTE 5 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRI-PLEN tablets:

Each film-coated tablet contains 2,5 mg of felodipine and 2,5 mg of ramipril.

Excipient(s) with known effect:

Each tablet contains sugar (52 mg lactose anhydrous).

For the full list of excipients, see section 6.1.

TRI-PLEN FORTE tablets:

Each film-coated tablet contains 5 mg of felodipine and 5 mg of ramipril.

Excipient(s) with known effect:

Each tablet contains sugar (52 mg lactose anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

TRI-PLEN: An apricot, circular, biconvex, film-coated tablet engraved H/OD on one side and 2,5 on the other side. The core is of double-layer type with white to off-white and yellow layers.

TRI-PLEN FORTE: A reddish-brown, circular, biconvex, film-coated tablet engraved H/OE on one side and 5 on the other side. The core is of double layer type with white to off-white and yellow layers.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate hypertension in patients whose blood pressure is normalised with individual components in the same doses as the proposed fixed combination.

4.2 Posology and method of administration

Posology

Adults, including elderly:

One TRI-PLEN tablet or one TRI-PLEN FORTE tablet once daily.

The maximum dose is one TRI-PLEN FORTE tablet once daily.

Special populations

Patients on diuretics:

Consideration should be given to temporarily discontinuing the diuretic or at least to reducing the dose 2 or 3 days before initiation of treatment with TRI-PLEN tablets (2,5 mg/2,5 mg). If this is not possible start with ramipril 1,25 mg daily and increase to ramipril 2,5 mg daily before transferring to TRI-PLEN tablets (2,5 mg/2,5 mg).

Patients with incompletely corrected fluid or salt depletion:

Start with ramipril 1,25 mg daily and increase to ramipril 2,5 mg daily before transferring to TRI-PLEN tablets (2,5 mg/2,5 mg).

Patients with severe hypertension or those in whom a hypotensive reaction would constitute a particular risk (e.g. those with significant stenoses of the coronary vessels or those vessels supplying the brain):

Start with ramipril 1,25 mg daily and increase to ramipril 2,5 mg daily before transferring to TRI-PLEN tablets (2,5 mg/2,5 mg).

Patients with impaired renal function:

Creatinine clearance 30 to 50 mL/min: start with ramipril 1,25 mg daily and increase to ramipril 2,5 mg daily before transferring to TRI-PLEN tablets (2,5 mg/2,5 mg). A maximum dose of ramipril 5 mg daily must not be exceeded.

Creatinine clearance below 30 mL/min and dialysis patients: no experience with ramipril (see section 4.3).

Patients with impairment of liver function:

There is no experience in the use of TRI-PLEN and TRI-PLEN FORTE in patients with severe impairment of the liver function. As both felodipine and ramipril are metabolised by the liver it is recommended that treatment in patients with impaired liver function be initiated with low doses of felodipine or ramipril under close medical supervision. The maximum permitted daily dose for ramipril in such cases is 2,5 mg and therefore TRI-PLEN (2,5 mg/2,5 mg) is the maximum dose in this patient group. TRI-PLEN FORTE (5 mg/5 mg) should not be used.

Children:

No experience is available. TRI-PLEN and TRI-PLEN FORTE should not be given to children.

Method of administration:

The tablets should be swallowed whole with a sufficient amount of liquid. The tablets must not be divided, crushed or chewed. The tablets can be administered without food or following a light meal not rich in fat or carbohydrate.

4.3 Contraindications

- hypersensitivity to felodipine (or other dihydropyridines), ramipril, other angiotensin converting enzyme (ACE) inhibitors or any of the excipients listed in section 6.1.
- a history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARB's): These patients must never again be given these medicines.

- hereditary or idiopathic angioedema.
- hypertrophic obstructive cardiomyopathy (HOCM).
- 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.
- porphyria.
- lithium therapy: concomitant administration with TRI-PLEN or TRI-PLEN FORTE may lead to toxic blood concentrations of lithium.
- unstable haemodynamic conditions: cardiovascular shock, untreated heart failure, acute myocardial infarction, unstable angina pectoris, stroke.
- patients with AV block II or III.
- severely impaired hepatic function.
- severe renal function impairment (creatinine clearance less than 30 mL/min).
- pregnancy and lactation.
- concomitant use of ACE inhibitors with fluoroquinolones is contraindicated in patients with moderate to severe renal impairment.
- concomitant use with sacubitril/valsartan therapy (see sections 4.4 and 4.5).
- the concomitant use of TRI-PLEN or TRI-PLEN FORTE with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).
- the concomitant use of TRI-PLEN or TRI-PLEN FORTE with an ARB is contraindicated (see sections 4.4 and 4.5).

Concomitant use of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided since it may lead to severe anaphylactoid reactions. Such extracorporeal treatments include dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitrile) membranes and low-density lipoprotein apheresis with dextran sulphate.

4.4 Special warnings and precautions for use

Angioedema

Angioedema occurring during treatment with an ACE inhibitor necessitates immediate discontinuation of the medicinal product. Angioedema may involve the tongue, glottis or larynx may be fatal. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous adrenaline solution 1:1 000 (0,3 to 0,5 mL) or slow intravenous adrenaline 1 mg/mL (observe dilution instructions) with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, facial angioedema also occurred. The intestinal angioedema symptoms stopped after stopping the ACE inhibitor.

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

Dual blockade of the renin-angiotensin-aldosterone system by combining TRI-PLEN or TRI-PLEN FORTE with an angiotensin-II receptor blocker (ARB) or with aliskiren is contraindicated since there are increased risks of hypotension, hyperkalaemia and change in renal function (including acute renal failure).

The use of TRI-PLEN or TRI-PLEN FORTE in combination with aliskiren is contraindicated (see sections 4.3 and 4.5).

The use of TRI-PLEN or TRI-PLEN FORTE in combination with an ARB is contraindicated (see sections 4.3 and 4.5).

Patients with a significantly activated renin-angiotensin system:

Caution should be observed in patients with an activated renin-angiotensin system. These patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor and a concomitant diuretic is given for the first time or for the first time at an increased dose. They therefore need close blood pressure monitoring until no further acute reduction in blood pressure is expected.

Significant activation of the renin-angiotensin system is to be expected in:

- patients with severe hypertension: Initiation of treatment with ACE inhibitor should preferably be carried out in hospital or similar setting.
- patients with concomitant moderate heart failure: Initiation of treatment with ACE inhibitor should preferably be carried out in hospital or similar setting.
- patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve, obstructive cardiomyopathy – see section 4.3): The initial phase of treatment requires special medical supervision.
- patients with haemodynamically relevant artery stenosis: Initiation of treatment with ACE inhibitor should preferably be carried out in hospital or similar setting (see section 4.3).
  Discontinuation of diuretic therapy may be required (see also below under “Monitoring of renal function”).
- patients on concomitant diuretic therapy.
- patients in whom fluid or salt depletion is present: If possible, the salt and/or fluid deficiencies should be corrected before initiation of therapy.

Monitoring of renal function:

Treatment with ramipril may impair renal function. Patients with renal insufficiency may require reduced or less frequent doses of ramipril and their renal function should be closely monitored, particularly in the initial weeks of treatment with ACE inhibitors.

Especially careful monitoring is required in patients with:

- concomitant heart failure.
- renovascular disease: Note that in patients with haemodynamically relevant unilateral renal artery stenosis even a small increase in serum creatinine may be indicative of unilateral loss of renal function (see section 4.3).
- impairment of renal function.
- kidney transplantation: There is no experience regarding the administration of TRI-PLEN and TRI-PLEN FORTE in patients with recent kidney transplantation.

Electrolyte monitoring/Hyperkalaemia:

Elevated serum potassium has been observed in some patients treated with ACE inhibitors, including ramipril. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium-sparing diuretics and the concomitant use of agents to treat hypokalaemia. It is recommended that serum potassium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function (see section 4.3).

Potassium-sparing diuretics, potassium supplements and other medicines that may increase serum potassium level increase the risk of hyperkalaemia, sometimes severe, and should, therefore, not be given together with TRI-PLEN and TRI-PLEN FORTE (see section 4.5).

Electrolyte monitoring/Hyponatremia

Treatment with TRI-PLEN or TRI-PLEN FORTE requires regular monitoring of serum sodium.

Patients with impairment of liver function:

As ramipril is a prodrug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied in patients with liver impairment. The metabolism rate of the parent compound and therefore the formation of the bioactive metabolite ramiprilat may be slower and result in markedly elevated plasma levels of the parent compound due to the diminished activity of esterases in the liver.

Patients with severe impairment of liver function: There is no experience in the use of TRI-PLEN and TRI-PLEN FORTE in patients with severe impairment of liver function. In patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin-angiotensin system may be significantly activated; therefore, particular caution must be exercised in treating these patients with TRI-PLEN or TRI-PLEN FORTE.

Symptomatic hypotension:

In some patients, symptomatic hypotension may be observed after the initial dose mainly in patients with heart failure (with or without renal insufficiency) treated with high doses of loop diuretics, in hyponatraemia or in reduced renal function. Therefore, TRI-PLEN and TRI-PLEN FORTE should only be given to such patients after special consideration and after the doses of the individual components have been carefully titrated. TRI-PLEN and TRI-PLEN FORTE should only be given if the patient is in a stable circulatory condition (see section 4.3). In hypertensive patients without cardiac and renal insufficiency, hypotension may occur especially in patients with decreased blood volume due to diuretic therapy, salt restriction, diarrhoea or vomiting.

Patients at particular risk from a pronounced reduction in blood pressure:

Patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with coronary or cerebrovascular insufficiency) should be treated with ramipril and felodipine in a free combination. If satisfactory and stable blood pressure control is achieved with the doses of ramipril and felodipine included in TRI-PLEN and TRI-PLEN FORTE, the patient can be switched to this combination. In some cases, felodipine may cause hypotension with tachycardia, which may aggravate angina pectoris.

Patients with haemodynamically relevant stenosis of the coronary arteries or of the blood vessels supplying the brain will require especially careful monitoring, preferably in a hospital or similar setting.

Haematological monitoring:

It is recommended that during ACE inhibitor therapy the white blood cell count is monitored so that a

possible leucopenia can be detected. More frequent monitoring is advised in the initial phase of treatment and the risk groups mentioned under section 4.4.

Neutropenia/Agranulocytosis:

TRI-PLEN and TRI-PLEN FORTE may cause agranulocytosis and neutropenia. These undesirable effects have also been shown with other ACE inhibitors, rarely in uncomplicated patients, but more frequently in patients with some degree of renal impairment, especially when it is associated with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma) and therapy with immunosuppressive agents. Monitoring of white blood cell counts should be considered for patients who have collagen vascular disease, especially if the disease is associated with impaired renal function. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Should symptoms such as fever, swelling of the lymph nodes, and/or inflammation of the throat occur in the course of therapy with TRI-PLEN and TRI-PLEN FORTE, the treating medical practitioner must be consulted and the white blood cell picture immediately investigated.

Cough:

During treatment with an ACE inhibitor a dry cough may occur which disappears after discontinuation (see section 4.8).

Concomitant use of ACE inhibitors and highly permeable dialysis membranes, haemofiltration, LDL apheresis and hyposensitisation with the venom of wasps or bees: Must be avoided since such use may lead to severe anaphylactoid reactions (see section 4.5).

Fluoroquinolones and ACE inhibitors:

Concomitant use of fluoroquinolones and ACE inhibitors 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 whether used separately and/or concomitantly.

Children, patients with creatinine clearance under 30 mL/min and dialysis-treated patients: No experience is available. TRI-PLEN and TRI-PLEN FORTE should not be given to these patient groups.

Gingival enlargement

Mild gingival enlargement has been reported in patients taking felodipine with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.

Some patients with no apparent pre-existing renal disease may develop increases in blood urea, proteinuria and serum creatinine when ramipril is given.

Neutropenia and proteinuria:

Haematological reactions to ACE inhibitors are more likely to occur in patients with impaired renal function and in those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), or in those treated with other medicines that may cause changes in the blood picture. Regular monitoring of white blood cell counts and protein levels in urine should be performed in patients with collagen vascular disease, such as lupus erythematosus and systemic sclerosis, in particular where associated with impaired renal function and concomitant therapy with medicines like corticosteroids and antimetabolites (see section 4.4).

Surgery/anaesthesia:

In patients undergoing surgery or during anaesthesia with agents producing hypotension, ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism it can be corrected by volume expansion.

Hypotension:

Hypotension may occur after the initial dose of ramipril as well as after increasing the dose of ramipril.

Symptomatic hypotension (i.e. headache, tiredness, palpitations, tinnitus) accompanied by dizziness, nausea and a feeling of weakness can be observed in salt/volume depleted patients such as those treated with diuretics or patients on dialysis as well as in patients with severe congestive heart failure. Syncope has been observed. In patients with concomitant congestive heart failure with or without renal insufficiency, excessive hypotension has been observed and may be associated with oliguria or azotaemia. In these patients, therapy should be started under close medical supervision, and at a reduced starting dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline.

Laboratory values – Ramipril:

- increases in blood urea and serum creatinine may occur, particularly in patients with renal insufficiency or in patients pre-treated with a diuretic. Elevation of serum potassium may occur, since ramipril decreases aldosterone secretion.
- increases in liver enzymes and/or bilirubin.
- changes in blood picture – decrease in haemoglobin, leukopenia and thrombocytopenia.

Lactose:

TRI-PLEN and TRI-PLEN FORTE contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take TRI-PLEN or TRI-PLEN FORTE.

4.5 Interaction with other medicines and other forms of interaction

Potassium salts, potassium-sparing diuretics or other medicines that may increase kalaemia:

Rise in serum potassium concentration, sometimes severe, is to be anticipated. Concomitant treatment with potassium-sparing diuretics (e.g. spironolactone, amiloride, triamterene), potassium salts, or other medicines that may increase kalaemia requires close monitoring of serum potassium.

Sacubitril/valsartan:

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

Aliskiren-containing medicines:

The combination of TRI-PLEN or TRI-PLEN FORTE with aliskiren containing medicines is contraindicated (see sections 4.3 and 4.4).

Angiotensin-II receptor blockers (ARBs):

The use of TRI-PLEN or TRI-PLEN FORTE in combination with an ARB is contraindicated (see sections 4.3 and 4.4).

Dual blockade 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, such as TRI-PLEN or TRI-PLEN FORTE, with an angiotensin-II receptor blocker (ARB) or aliskiren is not recommended as there are increased risks of hypotension, hyperkalaemia and changes in renal function (see sections 4.3 and 4.4).

Extracorporeal treatment:

Leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitrile) membranes and low-density lipoprotein apheresis with dextran sulphate: Risk of severe anaphylactoid reactions (see section 4.3).

Lithium:

Excretion of lithium may be reduced by ACE inhibitors leading to lithium toxicity. Lithium levels must, therefore, be monitored (see section 4.3).

Antihypertensive agents or other substances with blood pressure-lowering potential (e.g.

diuretics, antipsychotics, nitrates, anaesthetics and narcotics): Potentiation of the antihypertensive effect of TRI-PLEN or TRI-PLEN FORTE is to be anticipated. Concerning diuretics see sections 4.2 and 4.4.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture:

Increased likelihood of haematological reactions due to ramipril.

Enzyme inhibitors of the cytochrome P450 enzyme system (e.g. cimetidine, erythromycin, itraconazole, ketoconazole and certain flavonoids found e.g. in grapefruit juice):

Increase in the plasma levels of felodipine may be expected.

Enzyme inducers of the cytochrome P450 enzyme system [e.g. rifampicin, phenytoin, carbamazepine, barbiturates and *Hypericum perforatum* (St John's wort)]:

A decrease in the plasma levels of felodipine may be expected.

Tacrolimus:

Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed, and the tacrolimus dose may need to be adjusted.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Attenuation of the effect of ramipril is to be expected. Furthermore, concomitant administration of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Vasopressor sympathomimetics:

These may reduce the antihypertensive effect of TRI-PLEN or TRI-PLEN FORTE. Close blood pressure monitoring is recommended.

Insulins, metformin, sulphonylureas:

Concomitant treatment with ACE inhibitors and antidiabetic agents may cause a pronounced hypoglycaemic effect with the risk of hypoglycaemia. The effect is most pronounced at the beginning of treatment.

Fluoroquinolones:

Concomitant use of ACE inhibitors and fluoroquinolones 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).

Heparin:

Rise in serum potassium concentration possible.

Salt:

Increased dietary salt intake may attenuate the antihypertensive effects of TRI-PLEN and TRI-PLEN FORTE.

Alcohol:

Increased vasodilatation.

Food:

The absorption of felodipine and ramipril is not influenced by food intake.

Desensitisation therapy:

Increased likelihood and greater severity of anaphylactic and anaphylactoid reactions to insect venom under ACE inhibition (see section 4.4).

Vildagliptin:

An increased incidence of angioedema was found in patients taking ACE inhibitors and vildagliptin.

mTOR inhibitors (e.g. temsirolimus):

An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR inhibitors (mammalian target of rapamycin inhibitors).

Neprilysin (NEP) inhibitors:

An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitors (such as racecadotril).

4.6 Fertility, pregnancy and lactation

Pregnancy

TRI-PLEN or TRI-PLEN FORTE must not be taken during pregnancy (see section 4.3). Pregnancy must be excluded before initiation of treatment and it must be avoided during therapy with TRI-PLEN or TRI-PLEN FORTE.

Should women become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and switched to a different class of medicine. Should women contemplate pregnancy, the doctor should consider alternative medicine.

ACE inhibitors pass through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth-mass can occur. Infants exposed to ACE inhibitors *in utero* are to be closely monitored for hypotension, oliguria and

hyperkalaemia. If oliguria is present or developing, support of blood pressure and renal perfusion may be necessary.

Breastfeeding

TRI-PLEN or TRI-PLEN FORTE must not be taken by breastfeeding women (see section 4.3).

Fertility

No fertility data available.

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. some symptoms of reduction in blood pressure such as dizziness) may be accompanied by an impairment of the ability to concentrate and react. This may constitute a risk in situations where these abilities are of special importance, e.g. when driving a car or operating machinery.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common: ≥ 10 %; Common: ≥ 1 and < 10 %; Uncommon ≥ 0,1 and < 1 %; Rare: ≥ 0,01 and < 0,1 %; Very rare: < 0,01 %.

The following undesirable effects may occur in connection with felodipine treatment:

Immune system disorders

Very rare: hypersensitivity reactions e.g. angioedema, fever

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthesia

Cardiac disorders

Uncommon: tachycardia, palpitations

Rare: syncope

Vascular disorders

Common: flush

Uncommon: hypotension

Gastrointestinal disorders

Uncommon: nausea, abdominal pain

Rare: vomiting

Very rare: gingival hyperplasia, gingivitis

Hepatobiliary disorders

Very rare: increased liver enzymes

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus

Rare: urticaria

Very rare: photosensitivity reactions, leucocytoclastic vasculitis

Musculoskeletal and connective tissue disorders

Rare: arthralgia, myalgia

Renal and urinary disorders

Very rare: polyuria

General disorders and administration site conditions

Uncommon: fatigue

Reproductive system and breast disorders

Rare: impotence/sexual dysfunction.

The following undesirable effects may occur in connection with ramipril treatment

Blood and lymphatic system disorders

Rare: decreased white blood cell count (including neutropenia or agranulocytosis), decreased red blood cell count, decreased haemoglobin, decreased platelet count

Immune system disorders

Uncommon: angioedema with fatal outcome (may be/become life-threatening, rarely severe course can cause fatal obstruction)

Endocrine disorders

Not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

Common: blood potassium increased

Uncommon: anorexia, decreased appetite

Psychiatric disorders

Uncommon: depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence

Rare: confusional state

Nervous system disorders

Common: headache, dizziness

Uncommon: paraesthesia, ageusia, dysgeusia, drowsiness

Rare: tremor, balance disorder

Eye disorders

Uncommon: visual disturbances including blurred vision

Rare: conjunctivitis

Ear and labyrinth disorders

Uncommon: vertigo

Rare: impaired hearing, tinnitus

Cardiac disorders

Uncommon: myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, dysrhythmia, palpitations, peripheral oedema

Vascular disorders

Common: hypotension, orthostatic hypotension, syncope

Uncommon: flushing

Rare: vascular stenosis, hypoperfusion, vasculitis

Respiratory, thoracic and mediastinal disorders

Common: non-productive tickling cough, bronchitis, sinusitis, dyspnoea

Uncommon: bronchospasm including aggravated asthma, nasal congestion

Gastrointestinal disorders

Common: gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting

Uncommon: fatal pancreatitis, pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth

Rare: glossitis

Hepatobiliary disorders

Uncommon: increased hepatic enzymes and/or increased bilirubin conjugated

Rare: cholestatic jaundice, hepatocellular damage

Skin and subcutaneous tissue disorders

Common: rash in particular maculo-papular

Uncommon: pruritus, hyperhidrosis

Rare: exfoliative dermatitis, urticaria, onycholysis

Very rare: photosensitivity reaction

Musculoskeletal and connective tissue disorders

Common: muscle spasms, myalgia

Uncommon: arthralgia

Renal and urinary disorders

Uncommon: renal impairment including acute renal failure, increased urine output, worsening of a pre-existing proteinuria, increased blood urea, increased blood creatinine

General disorders and administration site conditions

Common: chest pain, fatigue

Uncommon: pyrexia

Rare: asthenia

Reproductive system and breast disorders

Uncommon: transient erectile impotence, decreased libido.

Post-marketing:

Blood and lymphatic system disorders

Bone marrow failure, pancytopenia, haemolytic anaemia, eosinophilia

Immune system disorders

Anaphylactic or anaphylactoid reactions, increased antinuclear antibody

Metabolism and nutrition disorders

Decreased blood sodium

Psychiatric disorders

Disturbance in attention

Nervous system disorders

Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, impaired psychomotor skills, burning sensation, parosmia

Vascular disorders

Raynaud's phenomenon, exacerbation of perfusion disturbances

Gastrointestinal disorders

Aphthous stomatitis

Hepatobiliary disorders

Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, aggravated psoriasis, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia

Reproductive system and breast disorders

Gynaecomastia, trans erectile impotence, reduced libido

General disorders and administration site conditions

Sweating, fatigue.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TRI-PLEN or TRI-PLEN FORTE is important. It allows continued monitoring of the benefit/risk balance of TRI-PLEN or TRI-PLEN FORTE. Health care 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 or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Signs and symptoms:

Overdosage may cause excessive peripheral vasodilatation with marked hypotension, bradycardia, shock, electrolyte disturbances and renal failure.

Management:

Primary detoxification by, for example, gastric lavage, administration of adsorbents and/or sodium sulphate (if possible, during the first 30 minutes). In case of hypotension, administration of α_1-adrenergic agonists and angiotensin II must be considered in addition to volume and salt substitution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1 Vasodilators, hypotensive medicines

The calcium antagonist felodipine and the ACE (angiotensin-converting enzyme) inhibitor ramipril both reduce blood pressure by vasodilatation. Calcium antagonists dilate the arteriolar beds while ACE inhibitors dilate both arterial and venous beds. Vasodilatation and reduction of blood pressure may lead to activation of the sympathetic nervous system and the renin-angiotensin system. ACE inhibition results in decreased plasma angiotensin II. The onset of the antihypertensive effect of a single dose of TRI-PLEN or TRI-PLEN FORTE is 1 to 2 hours. The maximum antihypertensive effect occurs within 2 to 4 weeks and is maintained on long-term therapy. The blood pressure reduction is maintained throughout the 24-hour dosage interval.

Felodipine:

Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular resistance via a direct inhibitory action on vascular smooth muscles. Due to the high degree of selectivity for smooth muscle in the arterioles, felodipine in therapeutic doses has no direct effect on cardiac contractility or conduction. The renal vascular resistance is decreased by felodipine. Normal glomerular filtration rate is unchanged. In patients with impaired renal function, glomerular filtration rate may increase. Felodipine possesses a mild natriuretic/diuretic effect.

Ramipril:

Ramiprilat, the active metabolite of the prodrug ramipril, is a potent and long-acting ACE (angiotensin-converting enzyme) inhibitor. In plasma and tissue, ACE catalyses the conversion of angiotensin I to the vasoconstrictor angiotensin II and also the breakdown of the vasodilator bradykinin. The vasodilatation induced by the ACE inhibitor causes a reduction in blood pressure pre-load and after-

load. Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in secretion of aldosterone. Ramipril reduces peripheral arterial resistance without major changes in renal plasma flow and glomerular filtration rate. In hypertensive patients, ramipril leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate. The onset of the antihypertensive effect of a single dose of ramipril is 1 to 2 hours, the peak effect occurs at 3 to 6 hours and the duration of action is 24 hours. The maximum antihypertensive effect occurs after 3 to 4 weeks. Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

5.2 Pharmacokinetic properties

Felodipine:

The felodipine layer is in an extended-release formulation. Felodipine is completely absorbed from the gastrointestinal tract after oral administration of felodipine ER (extended release), independent of food intake. Due to extensive first pass metabolism the systemic availability of felodipine is approximately 15 % in man and is independent of dose in the therapeutic dose range. Plasma concentrations are directly proportional to dose within the therapeutic dose range of 2,5 to 10 mg. The plasma protein binding of felodipine is approximately 99 %. It is bound predominantly to the albumin fraction. The average half-life of felodipine in the terminal phase is 25 hours. There is no significant accumulation during long-term treatment. Felodipine is extensively metabolised by the liver and all identified metabolites are haemodynamically inactive. About 70 % of a given dose is excreted as metabolites in the urine; the remaining fraction is excreted in the faeces. Less than 0,5 % of a dose is recovered unchanged in the urine. Felodipine is a high clearance substance with an average blood clearance of 1 200 mL/min. Blood clearance of felodipine is decreased with increasing age. Decreased clearance in elderly patients leads to higher plasma concentration of felodipine. Age only partly explains the inter-individual variation in plasma levels. With the ER formulation, the absorption phase is prolonged. Peak plasma concentrations are reached within 3 to 4 hours after administration of felodipine ER.

Ramipril:

The pharmacokinetic parameters of ramiprilat are calculated after intravenous administration of ramipril. Ramipril is metabolised in the liver, and aside from the active metabolite ramiprilat, pharmacologically inactive metabolites have been identified. The formation of active ramiprilat may be decreased in patients with impaired liver function. The metabolites are excreted mainly via the kidneys. The bioavailability of ramiprilat is approximately 28 % after oral administration of ramipril. After intravenous administration of 2,5 mg ramipril, approximately 53 % of the dose is converted to ramiprilat. A maximum serum concentration of ramiprilat is achieved after 2 to 4 hours. Absorption and bioavailability are not influenced by concomitant intake of food. The protein binding of ramiprilat is approximately 55 %. The distribution volume is approximately 500 litres. The effective half-life, after repeated daily dosage of 5 to 10 mg is 13 to 17 hours. Steady state is achieved after approximately 4 days. Renal clearance is 70 to 100 mL/min and total clearance is approximately 380 mL/min. Impaired renal function delays the elimination of ramiprilat and excretion in the urine is reduced.

Combination product:

In TRI-PLEN and TRI-PLEN FORTE, the pharmacokinetics of ramipril, ramiprilat and felodipine are essentially unaltered compared to the monoproducts, felodipine extended release tablets and ramipril tablets. Felodipine does not influence the ACE inhibition caused by ramipril. The fixed combination tablets are thus regarded as bioequivalent to the free combination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl methylcellulose

Iron oxide yellow E172 (CI 77492)

Lactose anhydrous

Pregelatinised maize starch

Microcrystalline cellulose

Sodium stearyl fumarate

Hydroxypropyl cellulose LF

Polyoxyl 40 hydrogenated castor oil

Propyl gallate

Sodium aluminium silicate

Iron oxide reddish-brown E172 (CI 77491)

Hydrogen peroxide 30 %

Paraffin

Polyethylene glycol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep blister in outer carton until required for use.

6.5 Nature and content of container

PVC/PVDC blisters: 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precaution for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER(S)

TRI-PLEN: 31/7.1/0677

TRI-PLEN FORTE: 31/7.1/0678

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

TRI-PLEN: 24 January 2000

TRI-PLEN FORTE: 21 January 2000

10. DATE OF REVISION OF THE TEXT

08 September 2023