Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Triapin 5mg/5mg prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of felodipine and 5 mg of ramipril.
Excipient(s) with known effect:
Each tablet contains 51.5 mg lactose anhydrous.
Each tablet contains 5.00 mg macrogolglycerol hydroxystearate (polyoxyl hydrogenated castor oil).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Triapin 5mg/5mg tablets are circular (diameter approx 9 mm), reddish-brown coloured, biconvex and engraved H/OE on one side and marked 5 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension. Triapin fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on felodipine or ramipril alone.

4.2 Posology and method of administration

Posology

Use in adults, including older people:
One tablet Triapin 5mg/5mg once daily. The maximum dose is one tablet Triapin 5mg/5mg once daily.

Special populations

Use in patients with impaired liver function:
See sections 4.3 and 4.4.

Use in patients with impaired renal function or patients already on diuretic treatment:
See sections 4.3 and 4.4.

Individual dose titration with the components can be recommended and when clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Paediatric population:
Triapin is not recommended for use in children due to a lack of data.

Method of administration

Triapin tablets should be swallowed whole with a sufficient amount of liquid. The tablets must not be divided, crushed or chewed.

The tablet 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.
• history of angioedema.
• concomitant use with sacubitril/valsartan therapy (see sections 4.4 and 4.5).
• unstable haemodynamic conditions: cardiovascular shock,untreated heart failure, acute myocardial infarction, unstable angina pectoris, stroke.
• haemodynamically significant cardiac valvular obstruction.
• dynamic cardiac outflow obstruction.
• AV block II or III.
• severely impaired hepatic function.
• severely impaired renal function (creatinine clearance less than 20 ml/min) and in patients on dialysis.
• pregnancy.
• lactation.
• The concomitant use of Triapin with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Angioedema
Angioedema occurring during treatment with an ACE inhibitornecessitates immediatediscontinuation of the medicinal product.Angioedemamay involve the tongue, glottis or larynx (e.g. swelling of the airways or tongue, with or without respiratory impairment) and, if so, may necessitate emergency measures.

Angioedema of the face, extremities, lips, tongue, glottis or larynx has been reported in patients treated with ACE inhibitors. Emergency therapy should be given including, but not necessarily limited to, immediate subcutaneous adrenalin solution 1:1000 (0.3 to 0.5 ml) or slow intravenous adrenalin 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 there was no prior history of facial angioedema and C1-esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Compared with non-black patients, a higher incidence of angioedema has been reported in black patients treated with ACE inhibitors.

This risk of angioedema may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). The combination of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.5).

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 increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal function
Renal functionshould be monitored, particularly in the initial weeks of treatment with ACE inhibitors. Caution should be observed in patients with an activated renin-angiotensin system.

Patients with mild to moderately impaired renal function (creatinine clearance 20-60 ml/min) and patients already on diuretic treatment: For dosage see the respective monoproducts.

Electrolyte Monitoring: Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, age (>70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium-retaining diuretics; or other active substances increasing potassium (e.g. heparin, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin); or condition such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Electrolyte Monitoring: Hyponatremia
Syndrome of Inappropriate Anti-diuretic Hormone secretion (SIADH) and subsequent hyponatremia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in older people and in other patients at risk of hyponatremia.

Proteinuria
It may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Renovascular hypertension/renal artery stenosis
There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis.

There is no experience regarding the administration of Triapin in patients with a recent kidney transplantation.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progress to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Patients with mild to moderately impaired liver function:
For dosage see respective monoproducts.

Surgery/Anaesthesia
Hypotension may occur in patients undergoing major surgery or during treatment with anaesthetic agents that are known to lower blood pressure. If hypotension occurs, it may be corrected by volume expansion.

Aortic stenosis/Hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve, obstructive cardiomyopathy). The initial phase of treatment requires special medical supervision.

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, Triapin should only be given to such patients after special considerations and after the doses of the individual components have been carefully titrated. Triapin 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 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 Triapin, the patient can be switched to this combination. In some cases, felodipine may cause hypotension with tachycardia, which may aggravate angina pectoris.

Neutropenia/Agranulocytosis
Triapin 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 erythematodes, 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 Triapin, the treating physician must be consulted and the white blood picture investigated immediately.

Cough
During treatment with an ACE inhibitor a dry cough may occur which disappears after discontinuation.

Concomitant treatmentwith ACE inhibitors and antidiabetics
Concomitant treatment with ACE inhibitors and antidiabetics (insulin and oral antidiabetics) may lead to an enhanced hypoglycaemic effect with the risk of hypoglycaemia. This effect may be most pronounced at the beginning of treatment and in patients with impaired renal function.

Felodipine is metabolised by CYP3A4. Therefore, combination with medicinal products which are potent CYP3A4 inhibitors or inducers should be avoided. For the same reason, the concomitant intake of grapefruit juice should be avoided (see section 4.5).

Lithium
The combination of lithium and ACE inhibitors is not recommended. (see section 4.5).

LDL-apheresis
Concomitant use of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces should 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.

Desensitisation therapy
Increased likelihood and greater severity of anaphylactic and anaphylactoid reactions to insect venom (e.g. bee and wasp) as for other ACE inhibitors.

Pregnancy
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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, ramipril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Children, patients with creatinine clearance under 20 ml/min and dialysis-treated patients
No experience is available. Triapin 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.

Lactose
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Macrogolglycerol hydroxystearate

This medicinal product contains macrogolglycerol hydroxystearate (polyoxyl hydrogenated castor oil). It may cause stomach upset and diarrhea.

Sodium content
This medicinal product contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions

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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Contraindicated associations

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4). Treatment with ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of Triapin.

Not recommended associations

Felodipine is a CYP3A4 substrate. Medicinal products that induce or inhibit CYP3A4 will have large influence on felodipine plasma concentrations.

Medicinal products that increase the metabolism of felodipine through induction of cytochrome P450 3A4 include carbamazepine, phenytoin, phenobarbital and rifampin as well as St John's wort (*Hypericum perforatum*). During concomitant administration of felodipine with carbamazepine, phenytoin, phenobarbital, AUC decreased by 93% and C_{max} by 82%. A similar effect is expected with St John's wort. Combination with CYP3A4 inducers should be avoided.

Potent inhibitors of cytochrome P450 3A4 include azole antifungals, macrolide antibiotics, telithromycin and HIV protease inhibitors. During concomitant administration of felodipine with itraconazole, C_{max} increased 8-fold and AUC 6-fold. During concomitant administration of felodipine with erythromycin, C_{max} and AUC increased approximately 2.5-fold. Combination with potent CYP3A4 inhibitors should be avoided.

Grapefruit juice inhibits cytochrome P450 3A4. Concomitant administration of felodipine with grapefruit juice increased felodipine C_{max} and AUC approximately 2-fold. The combination should be avoided.

Caution is recommended with concomitant use

Lithium
Excretion of lithium may be reduced by ACE inhibitors, leading to lithium toxicity. Lithium levels must, therefore, be monitored.

Antihypertensive agents and other substances with blood pressure lowering potential (e.g. nitrates, antipsychotics, narcotics, anaesthetics)
Potentiation of the antihypertensive effect of Triapin is to be anticipated.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture
Increased likelihood of haematological reactions.

Nonsteroidal anti-inflammatory drugs (NSAIDs)
Attenuation of the effect of ramipril is to be expected. Furthermore, concomitant treatment with ACE inhibitors and such medicinal products may lead to an increased risk of worsening of the renal function and an increase in serum potassium.

Vasopressor sympathomimetics
These may reduce the antihypertensive effect of Triapin. Particularly close blood pressure monitoring is recommended.

mTOR inhibitors or vildagliptin:
An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy (see section 4.4).

Neprilysin (NEP) inhibitors
An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril (see section 4.4).

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

Insulins, metformin, sulphonylureas
Concomitant treatment with ACE inhibitors and antidiabetic agents may cause a pronounced hypoglycaemic effect with the risk of hypoglycaemia. This effect is most pronounced at the beginning of treatment.

Theophylline
Concomitant administration of felodipine and oral theophylline reduces theophylline absorption by approximately 20%. This is probably of minor clinical importance.

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.

Medicinal products causing hyperkalaemia
Potassium salts, heparin, potassium-retaining diuretics and other active substances causing hyperkalaemia (e.g trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin). Hyperkalaemia may occur, therefore, close monitoring of serum potassium is required (see section 4.4).

Salt
Increased dietary salt intake may attenuate the antihypertensive effect of Triapin.

Alcohol
Increased vasodilatation. The antihypertensive effect of Triapin may increase.

4.6 Fertility, pregnancy and lactation

Pregnancy
Triapin is contra-indicated (see section, 4.3.) in pregnancy.
Calcium antagonists may inhibit contractions of the uterus during labour. Definite evidence that labour is prolonged in full-term pregnancy is lacking. Risk of foetal hypoxia may occur if the mother is hypotensive and perfusion of the uterus is reduced due to redistribution of the blood-flow through peripheral vasodilatation. In animal experiments, calcium antagonists have caused embryotoxic and/or teratogenic effects, especially in the form of distal skeletal malformations in several species.

Appropriate and well-controlled studies with ramipril have not been done in humans. ACE inhibitors cross the placenta and can cause foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Breast-feeding

In animals, ramipril is excreted in milk. No information is available on whether or not ramipril is excreted in human breast-milk. Felodipine is excreted in human breast-milk.

Women must not breast-feed during treatment with Triapin (see section 4.3).

Fertility
No data on male and female fertility in patients are available (see section 5.3).

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 frequencies used in the tables throughout this section are:
very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10 000, <1/1000) and very rare (<1/10 000), not known (cannot be estimated from the available data)

The following undesirable effects may occur in connection with felodipine treatment

Frequencies/ Organ System	**Very Common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Immune system disorders					Hypersensitivity reactions
Metabolism and nutrition disorders					Hyperglycaemia
Psychiatric disorders				Impotence/ sexual dysfunction	
Nervous system disorders		Headache	Dizziness, paraesthesiae	Syncope	
Cardiac disorders			Tachycardia, palpitations		
Vascular disorders		Flush	Hypotension		Leucocytoclastic vasculitis
Gastrointestinal disorders			Nausea, abdominal pain	Vomiting	Gingival hyperplasia, gingivitis
Hepatobiliary disorders					Increased liver enzymes
Skin and subcutaneous tissue disorders			Rash, pruritus	Urticaria	Photosensitivity reactions, angioedema
Musculoskeletal and connective tissue disorders				Arthralgia, myalgia	
Renal and urinary disorders					Pollakisuria
General disorders and administration site conditions	Peripheral oedema		Fatigue		Fever

The following undesirable effects may occur in connection with ramipril treatment

Frequencies/ Organ System	**Common**		**Uncommon**		**Rare**	**Very rare**	**Not Known**

Blood and lymphatic system disorders			Eosinophilia		White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Immune system disorders							Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Metabolism and nutrition disorders	Blood potassium increased		Anorexia, decreased appetite				Blood sodium decreased
Psychiatric disorders			Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence		Confusional state		Disturbance in attention
Nervous system disorders		Headache, dizziness	Vertig	Tremor, balance			Cerebral ischaemia

			o, paraesthesia, ageusia, dysgeusia	disorder			including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders			Visual disturbance including blurred vision	Conjunctivitis			
Ear and labyrinth disorders				Hearing impaired, tinnitus			
Cardiac disorders			Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhyt				

			hmia, palpitations, oedema peripheral				
Vascular disorders		Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis			Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea		Bronchospasm including asthma aggravated, nasal congestion				
Gastrointestinal disorders		Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exception	Glossitis			Aphtous stomatitis

			ally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth				
Hepatobiliary disorders			Hepatic enzymes an	Jaundice cholestatic, hepatocellular damage			Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very

			d/or bilirubin conjugated increased				exceptional).
Skin and subcutaneous tissue disorders		Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome, pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis		Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective		Muscle spasms, myalgia	Arthra				

tissue disorders			lgia				
Endocrine disorders							Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Renal and urinary disorders			Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increa				

			sed				
Reproductive system and breast disorders			Transient erectile impotence, libido decreased				Gynaecomastia
General disorders and administration site conditions		Chest pain, fatigue	Pyrexia	Asthenia			

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

Symptoms

Overdose 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 sympathomimetics and angiotensin II must be considered in addition to volume and salt substitution. Bradycardia or extensive vagal reactions should be treated by administering atropine.

No experience is available concerning the efficacy of forced diuresis, alteration in urine pH, haemofiltration, or dialysis in speeding up the elimination of ramipril or ramiprilat. If
dialysis or haemofiltration is nevertheless considered, see also under section 4.4.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensive drugs.ATC code:C09BB05.

Both the calcium antagonist felodipine and the ACE inhibitor ramipril reduce blood pressure by dilation of the peripheral blood vessels. Calcium antagonists dilate the arterial beds while ACE inhibitors dilate both arterial and venous beds. Vasodilatation and thereby reduction of blood pressure may lead to activation of the sympathetic nervous system and the renin-angiotensin system. Inhibition of ACE results in decreased plasma angiotensin II.
The onset of the antihypertensive effect of a single dose of Triapin is 1 to 2 hours. The maximum antihypertensive effect is achieved within 2 to 4 weeks and is maintained during long-term therapy. The blood pressure reduction is maintained throughout the 24-hour dosage interval. Morbidity and mortality data are not available.

Felodipine is a vascular selective calcium antagonist, which lowers arterial blood pressure by decreasing peripheral vascular resistance via a direct relaxant action on vascular smooth muscles. Due to its 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. The normal glomerular filtration rate is not influenced. In patients with impaired renal function, the glomerular filtration rate may increase. Felodipine possesses a mild natriuretic/diuretic effect and fluid retention does not occur.

Ramipril is a prodrug which hydrolyses to the active metabolite ramiprilat, 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 reduces blood pressure pre-load and after-load. Since angiotensin II also stimulates the release of aldosterone, ramiprilat reduces secretion of aldosterone. Ramipril reduced peripheral arterial resistance without major changes in renal plasma flow or glomerular filtration rate. In hypertensive patients, ramipril leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

General characteristics of the active substances

Felodipine ER (extended-release formulation):
The bioavailability is approximately 15% and is not influenced by concomitant intake of food. The peak plasma concentration is reached after 3 to 5 hours. Binding to plasma proteins is more than 99%. The distribution volume at steady state is 10 l/kg. The half-life for felodipine in the elimination phase is approximately 25 hours and steady state is reached after 5 days. There is no risk of accumulation during long-term treatment. Mean clearance is 1200 ml/min. Decreased clearance in older people leads to higher plasma concentrations of felodipine. Age only partly explains the interindividual variation in plasma concentration, however. Felodipine is metabolised in the liver and all identified metabolites are devoid of vasodilating properties. Approximately 70% of a given dose is excreted as metabolites in the urine and about 10% with the faeces. Less than 0.5% of the dose is excreted unchanged in the urine. Impaired renal function does not influence the plasma concentration of felodipine.

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.

Characteristics of the combination product
In Triapin the pharmacokinetics of ramipril, ramiprilat and felodipine are essentially unaltered compared to the mono products, felodipine ER tablets and ramipril tablets. Felodipine does not influence the ACE inhibition caused by ramiprilat. The fixed combination tablets are thus regarded as bioequivalent to the free combination.

5.3 Preclinical safety data

Repeated-dose toxicity studies performed with the combination in rats and monkeys did not demonstrate any synergistic effects.
Non-clinical data for felodipine and ramipril reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Reproduction toxicity
Felodipine: In investigations on fertility and general reproductive performance in rats, a prolongation of parturition resulting in difficult labour/increased foetal deaths and early postnatal deaths was observed. Reproduction toxicity studies in rabbits have shown a dose-related reversible enlargement of the mammary glands of the parent animals and dose-related digital anomalies in the foetuses.
Ramipril: Studies in rats, rabbits and monkeys did not disclose any teratogenic properties. Daily doses during pregnancy and lactation in rats produced irreversible renal pelvis dilatation in the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Hyprolose
Hypromellose
Iron oxides E172
Lactose anhydrous
Macrogol 6000
Macrogolglycerol hydroxystearate
Maize starch
Paraffin
Propyl gallate
Sodium aluminium silicate
Sodium stearyl fumarate
Titanium dioxide E 171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 ºC.

6.5 Nature and contents of container

PVC/PVDC blisters: 10, 14, 15, 21, 28, 30, 50, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/082/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 1998

Date of lastest renewal: 19 September 2007

10 DATE OF REVISION OF THE TEXT

June 2021