

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

TRIALIX 5mg/6mg Tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Ramipril 5.0 mg  
Piretanide 6.0 mg

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

Oblong, yellowish-white tablets marked with a score line.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of essential hypertension in patients who are insufficiently controlled with monotherapy and who have been stabilised on the individual components given in the same proportions (see sections 4.3, 4.4, 4.5 and 5.1).

### 4.2 Posology and method of administration

As a general rule, the treatment of hypertension should be started with one of the component substances at a low dosage which is then gradually increased (see section 4.3, 4.4, 4.5 and 5.1).

The fixed combination of 5 mg ramipril and 6 mg of piretanide should only be used in patients whose blood pressure has already returned to normal pressure under treatment with a free combination of ramipril and piretanide in the same amounts as those in the combination.

The usual dosage in patients in whom the combination treatment is indicated is 1 tablet TRIALIX daily. If the blood pressure does not respond adequately to the combination, the dosage of TRIALIX must not be increased: instead, the necessary

maintenance dose should be determined by further dose titration with the free combination.

Dosage in patients with moderate impairment of renal function (creatinine clearance 30-60 ml/minute) and the elderly; titration with the individual components should be done very carefully. The maintenance dose is ½ tablet of TRIALIX daily and the maximum dose is 1 tablet of TRIALIX daily.

TRIALIX can be taken independently of meals and should be swallowed with plenty of fluid. In general, it is recommended that the prescribed daily dose be taken as one dose in the morning.

### 4.3 Contraindications

TRIALIX must not be prescribed for patients with any of the following conditions:

- In patients with hypersensitivity to ramipril, any other ACE inhibitor, pirtanide, sulfonamides or any of the excipients of TRIALIX.
- In patients with a history of angioedema.
- Concomitantly with sacubitril/valsartan therapy (see Section 4.5). Do not initiate TRIALIX until sacubitril/valsartan is eliminated from the body. In case of switch from TRIALIX to sacubitril/valsartan, do not start sacubitril/valsartan until TRIALIX is eliminated from the body.
- Severe impairment of renal function (serum creatinine > 1.8mg/dl or creatinine clearance < 30 ml/min).
- Renal condition requiring dialysis.
- Renal artery stenosis, bilateral or unilateral in the single kidney.
- History of renal transplantation.
- Haemodynamically relevant stenosis of the aortic or mitral valve, or hypertrophic cardiomyopathy.
- In patients with hypotensive or haemodynamically unstable states.
- Untreated, non-compensated congestive heart failure.
- Primary hyperaldosteronism.
- In patients with severe impairment of liver function or primary liver disease.
- In patients with clinically relevant electrolyte metabolism disturbances which may worsen following treatment with TRIALIX (e.g., hyponatraemia, hypokalaemia).
- In patients with clinically relevant fluid depletion (hypovolaemia).
- The concomitant use of TRIALIX with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m<sup>2</sup>) (see sections 4.5 and 5.1).
- In pregnancy.
- In breastfeeding women.
- In children.

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

#### **4.4 Special warnings and precautions for use**

TRIALIX should only be used after careful consideration of the risks and benefits to the patient in the presence of the following conditions: in all cases, representative clinical and laboratory variables should be monitored regularly:

##### ***Angioedema – Head, Neck or Extremities***

Angioedema occurring during treatment with an ACE inhibitor necessitates immediate discontinuation of the drug.

Angioedema of the face, extremities, lips, tongue, glottis or larynx has been reported in patients treated with ACE inhibitors.

Emergency treatment of life threatening angioedema includes immediate administration of epinephrine (subcutaneous or slow intravenous injection) accompanied by monitoring of ECG and blood pressure. Hospitalization of the patient is advisable with observation for at least 12 to 24 hours and discharge only upon complete resolution of the symptoms.

##### ***Angioedema – Intestinal***

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 resolved after stopping the ACE inhibitor.

An increased risk of angioedema is possible with concomitant use of other drugs which may cause angioedema (See Section 4.3 and Section 4.5)

Insufficient experience has been gained concerning the use of TRIALIX in children, in patients with severe impairment of renal function (creatinine clearance below 20 ml/min per 1.73 m<sup>2</sup> body surface area), and in dialysis patients.

Treatment with TRIALIX requires regular medical supervision.

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 section 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.

The use of TRIALIX in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73m<sub>2</sub>) (see Section 4.3, 4.5 and 5.1).

***Patients with hyper-stimulated rennin angiotensin system***

Patients with a hyper-stimulated rennin-angiotensin system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition. Initial doses or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is to be anticipated.

Significant activation of the renin angiotensin system is to be anticipated, for example:

- In patients with severe and malignant hypertension. The initial phase of treatment requires close medical supervision.
- In patients with concomitant heart failure. If heart failure is severe, the initial phase of treatment requires close medical supervision.
- In patients pre-treated with diuretics. Where discontinuing use or reducing the dose of the diuretic is not possible, the initial phase of treatment requires close medical supervision
- In patients with haemodynamically relevant left – ventricular in flow or out flow impediment.
- In patients with haemodynamically relevant renal artery stenosis.
- In patients in whom fluid or salt depletion exist or may develop as a result of insufficient fluid or salt intake, or as a result, for example, diarrhoea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate.

**Patients at particular risk from a pronounced reduction in blood pressure.**

In patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with haemodynamically relevant stenoses of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical supervision.

**Eldery:**

Some elderly patients may be particularly responsive to ACE inhibitors. Evaluation of renal function at the beginning of treatment is recommended.

**Monitoring of renal function.**

It is recommended that renal function be monitored, particularly in the initial weeks of treatment. Particularly careful monitoring is required in patients with

- heart failure
- impairment of renal function

**Electrolyte Monitoring**

Treatment with TRIALIX requires regular monitoring of serum sodium, potassium, calcium, uric acid, and blood glucose. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

**Haematological monitoring**

It is recommended that the white blood cell count be monitored to permit detection of a possible leucopenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma) or those treated with other drugs that can cause changes in the blood picture.

In the presence of clinically relevant proteinuria (more than 1g/day) patients treated with TRIALIX need careful monitoring.

**Primary Hyperaldosteronism**

If ramipril + piretanide is used in a patient with primary hyperaldosteronism, then careful monitoring of plasma potassium level is required.

**Other monitoring**

Particularly careful monitoring is required in:

- Patients with gout
- Patients with impaired liver function

**4.5 Interaction with other medicinal products and other forms of interactions**

The following interactions should be considered:

**Food:**

Absorption of ramipril is not significantly affected by food.

### ***Contraindicated combinations***

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (See Section 4.3).

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulfate: Risk of severe anaphylactoid reactions (see Section 4.3 Contraindications). Therefore a different kind of dialysis membrane should be used in patients who need emergency dialysis or haemofiltration and patients should be switched to a treatment with an antihypertensive drug not belonging to the ACE-inhibitor class.

The combination of TRIALIX with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60ml/min/1.73m<sub>2</sub> (see section 4.3, 4.4 and section 5.1).

Angiotensin-II receptor antagonists (AIIAs): the use of TRIALIX in combination with an AIIA is contraindicated in patients with diabetic nephropathy and is not recommended in other patients (See section 3 and 4.4).

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 section 4.3, 4.4 and 5.1).

### ***Not recommended associations***

Potassium salts, potassium-retaining diuretics (e.g. spironolactone, amiloride, triamterene) or other medicinal products that may increase kalaemia: Rise in serum potassium concentration possible, sometimes severe. Concomitant treatment with potassium-retaining diuretics (e.g. spironolactone), with potassium salts or other medicinal products that may increase kalaemia, requires close monitoring of serum potassium.

Ototoxic drugs: (e.g. aminoglycoside antibiotics): Possible intensification of the harmful effect of ototoxic drugs on hearing (due to piretanide). Since resultant hearing disorders could be irreversible, those substances and TRIALIX must only be used concurrently, when there are compelling medical reasons.

### ***Precautions for use***

Antihypertensive agents and other substances with antihypertensive potential (e.g., nitrates, tricyclic antidepressants, anaesthetics): potentiation of the antihypertensive effect is to be anticipated

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of TRIALIX. Particularly close blood pressure monitoring is recommended. Furthermore, the effect of the vasopressor sympathomimetics may be attenuated by piretanide.

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

Lithium salts: Excretion of lithium may be reduced. Such reduction may lead to increased serum lithium concentrations (levels should be monitored regularly) and increased lithium toxicity

Oral antidiabetics and insulin: ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics. Piretanide may attenuate the effect of antidiabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of coadministration.

Vildagliptin: An increased incidence of angioedema was found in patients taking ACE Inhibitors and vildagliptin

Trimethoprim and in fixed dose combination with sulfamethoxazole (Co-trimoxazole) An increased incidence of hyperkalaemia was observed in patients taking ACE inhibitors and Trimethoprim and in fixed dose combination with sulfamethoxazole (Co-trimoxazole).

mTOR Inhibitors (e.g. temsirolimus, everolimus, sirolimus): An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR Inhibitors (mammalian target of rapamycin inhibitors). Caution should be used when starting therapy.

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

### ***Associations to be considered with attention***

Nonsteroidal anti-inflammatory drugs (e.g. indomethacin) and acetylsalicylic acid: Possible attenuation of the effect of TRIALIX as well as development of acute renal failure or an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Probenecid: Possible attenuation of the antihypertensive effect (due to piretanide)

Salicyclates: Possible intensification of the effect and the toxicity of salicylates.

Corticosteroids, ACTH, amphotericin, carbenoxolone, large amounts of liquorice, laxatives (in case of prolonged use), and other kaliuretic or potassium decreasing agents: increased risk of hypokalaemia.

Digitalis preparations: Possible intensification of digitalis toxicity as a result of changes in electrolyte concentrations (e.g. hypokalaemia, hypomagnesaemia)

Muscle relaxants of the curare type: increase and prolongation of the muscle-relaxant effects by piretanide (anaesthetists must be informed that the patient is taking TRIALIX).

Nephrotoxic drugs: Possible intensification of the harmful effect of nephrotoxic drugs on the kidney (due to piretanide).

Table salt: reduction of antihypertensive effects of TRIALIX.

Alcohol: ramipril may lead to increased vasodilation and thus potentiate the effect of alcohol.

Desensitization therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

#### **4.6 Fertility, pregnancy and lactation**

TRIALIX must not be taken during pregnancy. Pregnancy must be excluded before the treatment and adequate contraceptive measures must be taken during treatment. Pregnancy must be avoided in cases where changeover to a treatment regimen without ACE inhibitors and diuretics is not possible. Otherwise there is a risk of harm to the foetus.

TRIALIX must not be taken by nursing mothers. If there is no alternative treatment to TRIALIX, the patient must therefore stop breastfeeding in order to prevent the infant from ingesting small quantities of ramipril and piretanide with breast milk.

#### **4.7 Effects on ability to drive and use machines**

Treatment with TRIALIX requires regular medical supervision. The ability to drive vehicles, cross the road safely or operate machinery may be affected to different degrees by the occurrence of different reactions. This particularly applies to the initial stages of treatment if the patient is switched to another drug, or in combination with alcohol.



## 4.8 Undesirable effects

As TRIALIX is an antihypertensive, many of its adverse reactions are effects secondary to its blood-pressure-lowering action which results in adrenergic counter-regulation or organ hypoperfusion. Numerous other effects (e.g. effects on electrolyte balance, certain anaphylactoid reactions or inflammatory reactions of the mucous membranes) are due to the ACE inhibition or to other pharmacologic actions of ramipril or piretanide.

The following adverse reactions have been observed during treatment with TRIALIX, its constituents ramipril and piretanide, other ACE inhibitors, or comparable diuretics, and may, therefore, occur.

Adverse reactions frequency is defined using the following convention:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

### **Adverse reactions due to Ramipril:**

	<b><u>Common</u></b>	<b><u>Uncommon</u></b>	<b><u>Rare</u></b>	<b><u>Very rare</u></b>	<b><u>Not known</u></b>
<i>Cardiac disorders</i>		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
<i>Blood and lymphatic system disorders</i>		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis)red		Bone marrow failure, pancytopenia, haemolytic anaemia

			blood cell count decreased, haemoglobin decreased, platelet count decreased		
<i>Nervous system disorders</i>	Headache, dizziness (lightheadedness)	Vertigo, paraesthesia, ageusia (loss of taste), dysgeusia (taste disturbances)	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor or skills impaired (impaired reactions), burning sensation, parosmia (smell disturbances)
<i>Eye disorders</i>		Visual disturbance including blurred vision	Conjunctivitis		
<i>Ear and labyrinth disorders</i>			Hearing impaired, tinnitus		
<i>Respiratory, thoracic and mediastinal disorders</i>	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			

<i>Gastrointestinal disorders</i>	Gastrointestinal inflammation (inflammatory reactions of the gastrointestinal tract), digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Fatal pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis (inflammatory reactions of the oral cavity)
<i>Renal and urinary disorders</i>		Renal impairment including renal failure acute, urine output increased, worsening of pre-existing proteinuria, blood urea increased, blood creatinine increased			
<i>Skin and subcutaneous tissue disorder</i>	Rash in particular maculo-papular	Angioedema with fatal outcome (maybe/become life-threatening, rarely severe course can cause fatal	Exfoliative dermatitis, urticaria, onycholysis	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus,

		obstruction); pruritus, hyperhidrosis (sweating)			psoriasis aggravate d, dermatitis psoriasifor m, pemphigoid or lichenoid exanthema or enanthema, alopecia
<i>Musculoskel etal and connective tissue disorder</i>	Muscle spasms (muscle cramps), myalgia	Arthralgia			
<i>Endocrine disorders</i>					Syndrome of inappropri ate antidiuretic hormone secretion (SIADH)
<i>Metabolism and nutrition disorders</i>	Blood potassium increased	Anorexia, decreased appetite			Blood sodium decreased
<i>Vascular disorders</i>	Hypotension, orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope	Flushing	Vascular stenosis, hypoperfusi on (exacerbati on of perfusion disturbance s), vasculitis		Raynaud's phenomen on

<i>General disorders and administration site conditions</i>	Chest pain, fatigue	Pyrexia (fever)	Asthenia (weakness)		
<i>Immune system disorders</i>					Anaphylactic or anaphylactoid (severe anaphylactic and anaphylactoid reactions to insect venom) is increased under ACE inhibition), antinuclear antibody increased
<i>Hepatobiliary disorders</i>		Hepatic enzymes and/or bilirubin conjugated increased	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
<i>Reproductive system and breast</i>		Transient erectile impotence,			Gynaecomastia

<i>disorder</i>		libido decreased			
<i>Psychiatric disorders</i>		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness)	Confusional state		Disturbance in attention

**Adverse reactions due to Piretanide:**

	<b>Adverse Reaction</b>
<i>Blood and lymphatic system disorders</i>	Haemoconcentration
<i>Renal and urinary disorders</i>	Complaints in patients who suffer from urinary outflow impairment; development of fluid depletion
<i>Musculoskeletal and connective tissue disorders</i>	Muscular weakness; tetany
<i>Metabolism and nutrition disorders</i>	Increase in serum cholesterol and triglycerides; Development or aggravation of a metabolic alkalosis; increase of calcium and magnesium excretion; decrease in potassium concentration; increased serum concentrations of uric acid; lower tolerance to glucose; intensified thirst
<i>Vascular disorders</i>	Thrombosis
<i>Ear and labyrinth disorders</i>	Hearing disorders, such as tinnitus and deafness (sometimes irreversible) have been reported with loop diuretics

**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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## 4.9 Overdose

### Symptoms

Overdose may cause persistent diuresis, excessive peripheral vasodilation (with marked hypotension, shock), bradycardia, electrolyte disturbances, renal failure, cardiac arrhythmias, impairment of consciousness up to and including coma, cereberal convulsions, pareses and paralytic ileus.

In patients with obstruction of urinary outflow (e.g. from prostatic hyperplasia), sudden diuresis may induce acute urinary retention with overdistension of the bladder.

### Management

The patient should be closely monitored and the treatment should be symptomatic and supportive.

Primary detoxification by, for example, gastric lavage, administration of adsorbants, sodium sulfate (if possible during the first 30 minutes). In the event of hypotension, administration of  $\alpha_1$ -adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), which is usually available only in scattered research laboratories, must be considered in addition to volume and salt substitution. 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 contemplated, see also under 4.3 Contraindications.

Piretanide is hardly dialysable.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC Code: CO9 BA05.

TRIALIX has both antihypertensive and diuretic effects.

Ramipril and piretanide are used alone and in combination for the treatment of hypertension. The antihypertensive effects of the two substances are complementary.

### Mode of Action

#### Ramipril

Ramipril is converted into ramiprilat in the liver by esterases. Ramiprilat is an ACE inhibitor.

ACE is a peptidyl-dipeptidase which causes angiotensin I to be converted to the vasoconstrictor angiotensin II. Inhibition of ACE causes less of the vasoconstrictor angiotensin II to be formed in the tissues and plasma, which in turn leads to a decrease in aldosterone secretion. This may lead to an increase in serum potassium concentrations. Since the negative feedback mechanism between angiotensin II and the renin secretion mechanism is abolished, the plasma renin activity increases.

Since ACE also degrades bradykinin, a vasodepressor peptide, inhibition of ACE results in increased circulating and local kallikrein systems (and thereby to an activation of the prostaglandin system). It is possible that this mechanism is involved in the antihypertensive effect of the ACE inhibitors and is also partly responsible for some of their side effects.

In patients with hypertension, ramipril decreases the supine and standing blood pressure without a compensatory increase in heart rate.

In haemodynamic investigations, ramipril brought about a marked reduction in peripheral arterial resistance. In general, clinically relevant changes in renal plasma flow and glomerular filtration rate were not observed.

In most patients, the onset of the antihypertensive effect occurs about 1.5 hours after oral intake of ramipril and the maximum effect is usually reached between 5 and 9 hours after intake. In the recommended dosage, the antihypertensive effect persists for 24 hours. The maximum antihypertensive effect of a given ramipril dose is generally seen after 3-4 weeks treatment.

In the recommended daily dosage, the antihypertensive effects are maintained even during long-term treatment. An abrupt halt in therapy does not cause rebound hypertension.

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 pharmacodynamics 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.

### Piretanide

Piretanide is a loop diuretic. It acts by blocking the Na/K/2Cl<sup>-</sup> carrier in the ascending branch of the loop of Henle. This inhibits the reabsorption of sodium and chloride ions. The fractional excretion of sodium in this process may account for up to 35 % of the sodium filtered by the glomeruli. Secondary effects of the increased excretion of sodium are the increased excretion of urine (due to osmotic binding of water) and increased distal tubular K<sup>+</sup> secretion. The excretion of Ca<sup>2+</sup> and Mg<sup>2+</sup> ions is also increased. In addition to the loss of the electrolytes mentioned, decreased excretion of uric acid and changes in the acid-base equilibrium towards metabolic alkalosis may occur.

In addition to its diuretic effects, the antihypertensive effects of piretanide are attributed to the normalisation of a disturbed electrolyte balance, principally brought about by a reduction of the increased activity of free Ca<sup>2+</sup> in the cells of the arterial muscles in essential hypertension. This presumably reduces the increased contractility and response of the vessels to endogenous pressor substances such as the catecholamines. The reduction of the increased blood pressure parallel to the intracellular Ca<sup>2+</sup> activity (measured in erythrocytes) following administration of piretanide suggests this mechanism of action.

Piretanide also increases venous capacity, mediated by prostaglandins and independent of diuresis.

Whilst the diuretic effects generally appear rapidly i.e. within 1 hour of intake, and have subsided between 4 and 6 hours after intake, the onset of the antihypertensive

effect is gradual and become obvious after 1-2 weeks. Antihypertensive effects which persist for 24 hours can then be achieved with a single daily dose.

The glomerular filtration rate and renal plasma flow remain stable during treatment with piretanide.

## **5.2 Pharmacokinetic properties**

### Ramipril

Ramipril is rapidly absorbed following oral administration. Absorption remains practically unaffected by concomitant intake of food. Maximum plasma concentrations of ramipril are reached within 1 hour. Elimination is rapid with a half-life of about 1 hour. Once absorbed, ramipril is almost completely hydrolysed into the active metabolite ramiprilat, predominantly in the liver.

Maximum ramiprilat plasma concentrations are reached between 2 and 4 hours after oral administration of ramipril. Ramiprilat is eliminated in several phases. During the distribution and elimination phase, the ramiprilat plasma concentrations decrease with a half-life of about 3 hours. This is followed by a transitional phase with a half-life of about 15 hours, and then a long terminal phase with a half-life of between 4 and 5 days, during which time the plasma ramiprilat concentrations are very low. The long terminal phase is due to the slow dissociation of ramipril from the tight but saturable bond to the conversion enzyme. A half-life for the dissociation process of 10.7 hours was calculated from in vitro experiments. Despite the long terminal half-life, the steady state with constant ramiprilat concentration is reached after about 4 days with repeated daily doses of 2.5mg ramipril or more. After repeated doses, therefore, the effective half-life, which is relevant for dosage, lies between 13 and 17 hours.

The volume of distribution of ramipril is about 90 litres and the relative volume of distribution of ramiprilat is about 500 litres. Serum protein binding of ramipril is about 73% and 56% for ramiprilat.

The bioavailability of ramipril lies between 15% for 2.5mg ramipril and 28% for 5mg ramipril. The bioavailability of the active ramiprilat following oral administration of 2.5 or 5mg ramipril is about 45% compared with the same doses of ramipril given intravenously.

The renal excretion of ramiprilat is decreased in the presence of impaired renal function (creatinine clearance < 60 ml/min). Renal clearance of ramiprilat decreases in proportion to creatinine clearance.

This results in increased plasma concentrations of ramiprilat which decrease more slowly than in patients with normal renal function.

In patients with impaired liver function in high doses (10 mg), the conversion of ramipril to ramiprilat is delayed and ramiprilat is eliminated more slowly.

In patients with heart failure treated for 2 weeks with 5mg ramipril daily, ramiprilat plasma concentrations and AUC values were 1.5 - 1.8 times higher than in patients not suffering from heart failure.

Ramipril and ramiprilat pharmacokinetics were similar in elderly (65 - 76 years) and young healthy subjects.

Following oral administration of radiolabelled ramipril, 39% of the radioactivity was recovered in the faeces and about 60% in the urine, 50 - 60% of the ramipril dose and its metabolites were recovered in the urine also following intravenous administration. After intravenous administration of ramiprilat, about 70% of the dose was recovered in the urine as ramiprilat and its metabolites. Nonrenal clearance accounted for 50 and 30% of the excretion of ramipril and ramiprilat respectively after intravenous administration. In patients with gall bladder drains, almost equal proportions of a dose of 5mg ramipril were found in the urine and bile after 24 hours.

Because of the marked first-pass biotransformation of ramipril following oral intake, only very small amounts of unchanged substance are found in the urine. In addition to metabolisation into ramiprilat, ramipril is also converted to the inactive diketopiperazine and is glucuronised. Ramiprilat is also glucuronised and is converted to diketopiperazinic acid. With the exception of ramiprilat, all metabolites and ramipril itself have no pharmacological activity.

#### Piretanide

Piretanide is rapidly absorbed following oral administration. The maximum serum concentration is reached about 1 hour after intake.

The bioavailability of piretanide amounts to between 80 and 90% in subjects with normal and impaired renal function. Interindividual and intraindividual variation is comparatively small.

The elimination half life of piretanide is about 1 - 1.7 hours in patients with normal renal function and up to 9 hours in patients with impaired renal function. Accumulation has not been observed in either subjects with normal renal function or patients with impaired renal function.

Serum protein binding of piretanide is about 90%.

Piretanide is excreted mainly as parent substance. It is principally excreted via the kidney and between 40 and 70% of the administered dose is recovered in the urine

in patients with normal renal function. Renal excretion is primarily via active secretion in the proximal tubule.

A few hydroxylated metabolites are found in the urine and faeces in the form of conjugates. The principal metabolite is a gamma aminobutanol derivative of piretanide.

Adjustment of the dose in elderly patients is not usually necessary.

#### Ramipril and piretanide in the ratio 5:6

The maximum serum concentrations (C<sub>max</sub>) of ramipril and ramiprilat and the areas under the concentration-time curves (AUC) were slightly higher when ramipril and piretanide were administered together. Urinary recovery of ramiprilat was increased but the total recovery of ramipril and its metabolites in the urine remained unchanged.

The maximum serum concentrations (C<sub>max</sub>) of piretanide was slightly decreased by co-administration of ramipril. The AUC, the time to reach the maximum serum concentration (t<sub>max</sub>) and the elimination half-life (t<sub>1/2</sub>) were, however, not affected. Urinary recovery of piretanide was not altered significantly.

These slight differences in the pharmacokinetics of the two substances when administered together did not alter the Pharmacodynamic effects of ramipril or piretanide.

### **5.3 Preclinical safety data**

#### Ramipril

Acute toxicity:

The oral LD<sub>50</sub> value for ramipril in the rat is higher than 10,000 mg/kg body weight. This means that acute administration of ramipril is completely non-toxic. The symptoms of acute intoxication are unspecific. Acute administration of ramipril to the beagle (LD<sub>50</sub> of 1,000 mg/kg body weight) is also non-toxic.

Chronic toxicity:

Trials with ramipril were conducted in the rat, dog and monkey. Chronic administration to rats in daily doses of about 40 mg/kg weight resulted in anaemia and electrolyte imbalance in the plasma. From doses of 3.2 mg/kg body weight upwards, evidence of incipient morphological changes in the kidney (atrophy of the distal tubule) was observed. These effects can be explained by the pharmacodynamic action of the ACE inhibitors. The tubular atrophy was observed only in the rat and not in the dog or monkey.

Marked enlargement of the juxtaglomerular apparatus, in particular in doses from 250mg/kg body weight/day upwards, was observed in the nonrodent species dog and monkey. This can be seen as indirect evidence of the pharmacodynamic activity of ramipril in inhibiting ACE (increased renin production).

Indications of changes in blood picture and electrolyte imbalance were also found in the dog and monkey.

Carcinogenic and mutagenic potential:

Long-term investigations with ramipril in the mouse and rat showed no neoplastic effects. Oxyphile cells in the renal tubules were observed after relatively high per kg body weight dosages of ramipril. This occurred principally in male rats and correlates with the age-dependent functional and morphological changes which occur during chronic renal failure. A comprehensive series of mutagenicity trials in several organ systems showed negative results.

Reproduction toxicity:

No teratogenic properties were observed in reproduction toxicity trials conducted in the rat, rabbit and monkey.

Administration of ramipril to rats during the period of fetal development and during lactation resulted in non-reversible renal lesions in the offspring (enlargement of the renal pelvis) from doses of 10mg/kg body weight/day upwards.

No adverse effects on fertility in male or female rats were observed. Ramipril passed into mother's milk in animals.

In the past few years, cases of a foetal syndrome characterised by severe hypoplasia of the cranium, intrauterine retardation of growth, oligohydramnios and neonatal anuria have been reported. Some newborns have died as a result of this. The syndrome is presumed to be due to the hypotensive effects on the foetus during the 2nd and 3rd trimester of the pregnancy.

No clinical experience with the use of ramipril in nursing mothers has been gathered.

Immune toxicology:

There were no relevant findings with ramipril in immune toxicity tests.

## Piretanide

### Acute toxicity:

No peculiarities were observed in acute toxicity trials in the rat, mouse, guinea pig, rabbit or dog. After oral administration, the LD50 in rats and mice was in the range of several grams, in the rabbit it was 1.25mg/kg body weight, and only in the guinea pig was it 93.2mg/kg body weight.

### Subchronic and chronic toxicity:

Dose-dependent, but reversible, haemoconcentration and calcification of the tubules were observed in rats treated for 30 days (40mg and 400mg piretanide/kg body weight/day).

Dogs treated with 1.25 and 16mg piretanide/kg body weight/day for 30 days developed striated atrophy of the renal parenchyma. Changes in the bones as signs of decalcification were also observed.

All substance-related pathological findings in beagles treated for 12 months orally with 0.05, 0.8 and 12.5mg piretanide/kg body weight/day occurred only in the highest dose group. This dose is 100 times higher than the therapeutic dose recommended in man and 250 times higher than the diuretic threshold dose in the dog.

Serum urea-nitrogen was significantly increased after the highest dose, and PAH and insulin clearance were decreased. The serum calcium concentrations were increased in the first 6 weeks, which can be interpreted as a sign of increased mobilisation of calcium.

This is also supported by the occurrence of reactive hyperplasia of the parathyroid gland and histological signs of alterations in bone metabolism. Species-specific foci of mainly subcapsular degenerative changes in the renal parenchyma also occurred after the highest dose.

Rhesus monkeys were treated for 1 year with 0.4, 2.0 and 10.0mg/kg piretanide/day. Only the highest dose produced pathological changes in some of the animals which could be attributed to excessive diuresis: bone changes attributable to mobilisation of calcium and very slight to marked renal lesions.

Chronic toxicity trials in the rat, dog and monkey showed that piretanide has a very wide therapeutic range.

### Carcinogenic and mutagenic potential:

None of the trials carried out in the mouse or rat showed any carcinogenic effects with piretanide. Mutagenicity trials in several systems were all negative.

### Reproduction toxicity:

Reproduction toxicity trials with oral and intravenous administration of piretanide to the mouse, rat and rabbit were conducted. None of the trials gave any indication of adverse effects on fertility, pregnancy, or foetal or postnatal development of the offspring.

### Ramipril and piretanide in the ratio 5:6

#### Acute toxicity:

The oral LD50 in the rat is 5414mg/kg body weight, which indicates that single doses of the combination were non-toxic. No synergistic effects of the two substances were observed.

#### Subchronic and chronic toxicity:

Rats were treated for 3 months with the combination in doses of 0.66, 1.1, 5.0 and 22.0mg/kg body weight/day orally. All animals survived, but showed reduced weight gain.

In female animals, decreased erythrocyte, haemoglobin and haematocrit levels were observed (only after 22mg/kg body weight/day) and increased serum urea levels were found (after 5 and 22mg/kg body weight/day). Levels returned to normal after the end of treatment. Isolated signs of tubular atrophy were observed in the high-dose groups (after 5 and 22mg/kg body weight/day).

There were also rare reports of calcification of the tubules after piretanide.

All the findings made with the combination in rats were also observed during toxicity testing with the individual components. There was no indication of a toxicological interaction between ramipril and piretanide in the sense that the effects of one potentiated those of the other.

Monkeys were treated for 3 months with the combination of ramipril and piretanide in doses of 1.1, 4.4 and 17.6mg/kg body weight/day. Food intake decreased dose-dependently and the body weight decreased. Erythrocytes and haemoglobin decreased under the highest dose, whilst serum area under the curve levels increased.

Levels returned to normal after the end of treatment. Histological investigations showed reversible dose-dependent hyperplasia of the juxtaglomerular cells in the afferent arterioles of the kidney as a manifestation of the effects of ramipril in the 4.4 and 17.6mg/kg body weight/day dose groups.

Carcinogenic and mutagenic potential:

Neither carcinogenicity nor mutagenicity trials were carried out for the combination since testing of the individual components had revealed no such potential.

Reproduction toxicology:

In embryo toxicity investigations, rats were treated orally in the sensitive phase of organogenesis, initially for dose-finding purposes with doses of 75 to 1000mg/kg body weight/day. Deaths occurred in all dosage groups.

In order to permit conclusions on possible teratogenic effects, the combination was given in a subsequent investigation to rats in a dosage of 37.5mg/kg body weight/day. There were no indications of teratogenic effects and no deaths occurred.

Treatment with the combination of ramipril and piretanide at a dosage of 0.55mg/kg body weight/day in rabbits in the sensitive phase of organogenesis led to only a slight delay in weight gain in the dams. No adverse effects however were observed on intrauterine development or the viability of the foetuses in the 24 hours after birth. At a dosage of 1.1mg/kg body weight/day, the food and fluid intake and the weight gain in the dams were decreased and the kidney weights increased. Also, deaths, abortions and premature births occurred. The live foetuses showed slight growth retardation. The survival rate was lower and the number of foetuses with a thirteenth rib was slightly increased.

Overall, the investigations in the rat and rabbit showed that the combination is somewhat more toxic than the individual components, although there was no indication of teratogenic effects.

Rats were treated in a perinatal and postnatal tolerance study with daily doses of 18.75mg/kg body weight/day orally in the third trimester of the pregnancy and in the three week lactation period. The dams showed a slight reduction in food intake. The size of the foetuses was decreased at birth. However, the animals developed normally in the postnatal period.

Investigations into possible impairment of fertility and reproduction were not carried out with the combination since no toxic effects were expected on the basis of the findings made with the individual components.



## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Hypromellose,  
Pregelatinised starch,  
Microcrystalline cellulose,  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

### **6.5 Nature and contents of container**

PVC/Al blister strip and type III amber glass bottle with PE or PP screw cap.

Pack size: 28 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 Ltd. T/A SANOFI  
Citywest Business Campus  
Dublin 24  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0540/081/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18<sup>th</sup> May 1995

Date of last renewal: 18<sup>th</sup> May 2010

**10 DATE OF REVISION OF THE TEXT**

December 2018