

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellisin 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg lisinopril as lisinopril dihydrate

Each tablet contains 50.0mg of excipient Mannitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Light yellow coloured, capsule shaped, biconvex uncoated tablets debossed with ‘1’ and ‘0’ on either side of the scoreline and a deep scoreline on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

Acute myocardial infarction

Short-term treatment (6 weeks) of haemodynamically stable patients in the 24 hours following acute myocardial infarction.

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 Posology and method of administration

Bellisin tablets should be administered orally as a single daily dose. As with all drugs taken once a day, Bellisin tablets should always be administered at approximately the same time. The consumption of food does not affect absorption of Bellisin tablets.

Dosage should be adjusted on an individual basis according to patient profile and arterial pressure response (see section 4.4)

Hypertension

Bellisin tablets may be used as monotherapy or in combination with other classes of antihypertensive drugs (see sections 4.3, 4.4, 4.5 and 5.1).

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a highly activated renin-angiotensin-aldosterone system (specifically patients with renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may suffer an excessive fall in arterial pressure after the initial dose. In

such patients a starting dose of 2.5-5 mg is recommended and treatment should be introduced under medical supervision. In the event of renal impairment, a lower starting dose is required (see Table 1 below).

Maintenance dose

The usual effective maintenance dose is 20 mg, administered as a single daily dose. In general, if the desired therapeutic effect cannot be achieved within a period of 2 to 4 weeks with a given dosage level, the dose may be increased. The maximum dose used in controlled long-term clinical trials was 80 mg/day.

Patients treated with diuretics

After starting treatment with Bellisin tablets, symptomatic hypotension may occur. This is more likely in patients who are receiving simultaneous diuretic treatment. Caution is therefore recommended; as such patients maybe volume and/or salt depleted. If possible, the diuretic should be withdrawn 2 to 3 days before starting treatment with Bellisin tablets. In hypertensive patients who cannot stop taking the diuretic treatment, treatment with Bellisin tablets should begin with a dose of 5 mg; renal function and blood potassium concentrations should be monitored. Subsequent Bellisin tablets dosage should be adjusted according to arterial pressure response. If necessary, diuretic treatment may be resumed (see section 4.4 and section 4.5).

Dosage adjustment in renal impairment

Dosage in patients with renal impairment should be based on creatinine clearance, as outlined in Table 1 below.

Table 1. Dosage adjustment in renal impairment

Creatinine clearance (ml/min)	Starting dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg/day

*Dose and/or frequency of administration should be adjusted according depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40mg daily.

Use in Hypertensive Paediatric Patients aged 6-16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see section 5.1).

In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Heart Failure

In patients with symptomatic heart failure, Bellisin tablets should be used as adjuvant treatment to diuretics and, where appropriate, digitalic agents or beta-blockers. Treatment may begin with a starting dose of 2.5 mg once a day, which should be administered under medical supervision in order to determine the initial effect on arterial pressure. Bellisin tablets dosage should be increased:

- by increments of not more than 10 mg;
- at intervals of not less than two weeks;
- to the highest dose tolerated by the patient, up to a maximum of 35 mg once a day.

Dosage adjustment should be based on the clinical response of individual patients.

In patients with a high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatraemia, hypovolaemia or who have been receiving intensive diuretic treatment, these problems should if

possible be corrected before starting treatment with Bellisin tablets. Renal function and serum potassium concentration should be monitored (see section 4.4).

Posology in Acute myocardial infarction

Patients should receive, as appropriate, the treatments usually recommended, such as thrombolytic agents, aspirin and beta blockers. Intravenous or transdermal nitroglycerin may be used together with Bellisin tablets.

Starting dose (first three days after the infarction)

Treatment with Bellisin tablets may begin in the 24 hours following the onset of symptoms. Treatment should not be introduced if systolic arterial pressure is less than 100 mmHg. The first dose of Bellisin tablets is 5 mg administered orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and, thereafter, 10 mg once a day. Patients with low systolic arterial pressure (120 mmHg or less) when treatment begins or during the first three days after the infarction should receive a lower dose: 2.5 mg orally (see section 4.4).

In the event of renal insufficiency (creatinine clearance <80 ml/min) the starting dose of Bellisin tablets should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once a day. If hypotension occurs (systolic arterial pressure less than or equal to 100 mmHg), a daily maintenance dose of 5 mg may be administered, with temporary decreases to 2.5 mg if necessary. If prolonged hypotension occurs (systolic arterial pressure less than 90 mmHg for more than one hour), Bellisin tablets should be withdrawn.

Treatment should continue for six weeks, after which the patient should be reassessed. Patients who develop symptoms of cardiac insufficiency should continue with Bellisin tablets (see section 4.2).

Renal complications of diabetes mellitus

In hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg of Bellisin tablets once a day. This dose may be increased to 20 mg once a day if necessary in order to achieve seated diastolic pressure of less than 90 mmHg.

In the event of renal impairment (creatinine clearance <80 ml/min), the starting dose of Bellisin tablets should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric population

There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications (see section 5.1). Lisinopril is not recommended in children in other indications than hypertension.

Lisinopril is not recommended in children below the age of 6, or in children with severe renal impairment (GFR <30ml/min/1.73m²) (see section 5.2).

Older people

In clinical studies there were no age-related changes in the efficacy and safety profile of the drug. However, when advanced age is associated with a decrease in renal function, the guidelines shown in Table 1 should be used to determine the starting dose of Bellisin tablets. The dose should be adjusted subsequently according to arterial pressure response.

Use in kidney transplant patients

There is no experience of administration of Bellisin tablets in recent kidney transplant patients. Treatment with Bellisin tablets is therefore not recommended.

4.3 Contraindications

- Hypersensitivity to Bellisin tablets, to any of the excipients as listed in section 6.1 or to any other angiotensin

- converting enzyme (ACE) inhibitor.
- History of angioedema associated with prior treatment with an ACE inhibitor.
- Hereditary or idiopathic angioedema
- Second or third trimesters of pregnancy (see sections 4.4 and 4.6)

The concomitant use of Bellisin tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension has occasionally been observed in uncomplicated hypertensive patients. In hypertensive patients treated with Bellisin tablets, hypotension is more likely if the patient is suffering from volume depletion due, for example, to diuretic therapy, a low-salt diet, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed; this is more likely in those patients with more severe grades of heart failure, reflected in the use of high doses of loop diuretics, hyponatraemia or impaired renal function. In patients with a high risk of symptomatic hypotension, the introduction of treatment and dosage adjustment should be monitored under close medical supervision. Similar considerations are applicable to patients with ischaemic heart or cerebrovascular disease in whom an excessive decrease in arterial pressure could cause myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine decubitus position and, if necessary, should receive an intravenous perfusion of physiological serum. A transient hypotensive response is not a contraindication to subsequent doses, which can usually be administered without difficulty, as arterial pressure increases following volume expansion.

In some patients with heart failure with normal or low arterial pressure, an additional decrease in systemic arterial pressure may occur with Bellisin tablets. This effect is expected and is not usually a reason to withdraw treatment. If the hypotension becomes symptomatic it may be necessary to reduce the dose or withdraw Bellisin tablets.

Hypotension in acute myocardial infarction

Treatment with Bellisin tablets should not be started in patients with acute myocardial infarction who run a serious risk of additional haemodynamic deterioration following treatment with a vasodilator. These are patients with systolic arterial pressure of 100 mmHg or less or in cardiogenic shock. During the first three days following the infarction the dose should be reduced if systolic arterial pressure is 120 mmHg or less. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic arterial pressure is 100 mmHg or less. If hypotension persists (systolic arterial pressure less than 90 mmHg for more than one hour) then treatment with Bellisin tablets should be withdrawn.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, Bellisin tablets should be administered with caution in patients with mitral valve stenosis and left ventricle outflow obstruction, as in aortal stenosis or hypertrophic cardiomyopathy.

Impaired renal function

In the event of renal impairment (creatinine clearance <80 ml/min), the starting dose of Bellisin tablets should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2.), and subsequently according to response to treatment. Systematic monitoring of blood potassium and creatinine concentrations forms part of normal medical practice in such patients.

In patients with heart failure, hypotension following the introduction of treatment with ACE inhibitors may cause additional impairment of renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery in a single kidney who have been treated with ACE inhibitors, increases in blood urea and serum creatinine concentrations, usually reversible on withdrawal of the treatment, have been observed. This is especially likely in patients with renal insufficiency. If renovascular

hypertension is also present there is a greater risk of severe hypotension and renal insufficiency. In such patients treatment should be introduced under strict medical supervision with low doses and careful dosage adjustment. As treatment with diuretics may be a contributing factor to what is described above, administration of diuretics should be halted and renal function should be monitored during the first few weeks of treatment with Bellisin tablets.

Some hypertensive patients, with no apparent pre-existing renovascular disease, have developed increases in blood urea and serum creatinine concentrations, usually slight and transient, especially when Bellisin tablets was administered concomitantly with a diuretic. This is more likely in patients with pre-existing renal impairment and it may be necessary to reduce the dosage and/or withdraw the diuretic and/or Bellisin tablets.

In acute myocardial infarction, treatment with Bellisin tablets should not be started in patients with signs of renal dysfunction, defined as serum creatinine concentration greater than 177 micromol/l and/or proteinuria above 500 mg/24 hours. If such renal dysfunction develops during treatment with Bellisin tablets (serum creatinine concentration greater than 265 micromol/l or twice the pre-treatment value) then the doctor should consider withdrawal of Bellisin tablets.

Hypersensitivity/Angioedema

There have been occasional reports of angioedema of the face, extremities, lips, tongue, glottis and/or larynx in patients treated with angiotensin converting enzyme inhibitors, including Bellisin tablets. This may occur at any time during treatment. In such cases, treatment with Bellisin tablets should be withdrawn immediately and appropriate treatment and monitoring established to ensure complete resolution of symptoms before patients are discharged. Even in cases in which only swelling of the tongue is observed, without respiratory difficulty, patients may need prolonged observation, as treatment with anti-histaminic agents and corticoids may not be sufficient.

There have been very rare reports of deaths due to angioedema associated with oedema of the larynx or tongue. Patients whose tongue, glottis or larynx is affected are liable to suffer airway obstruction, especially those who have previously undergone surgery on the airway. In such cases emergency treatment should be administered immediately. Such treatment may consist of administration of adrenaline and/or maintenance of a patent airway. The patient should remain under close medical surveillance until complete and maintained resolution of symptoms.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in patients of black race than in non-black patients.

Patients with a history of angioedema not related to ACE inhibitor therapy may increase the risk of angioedema when they are treated with this group of drugs (see section 4.3.).

Anaphylactoid reactions in haemodialysis patients

There have been reports of anaphylactoid reactions in patients undergoing dialysis with high-flux membranes (e.g. AN 69) treated simultaneously with an ACE inhibitor. In such patients use of a different type of dialysis membrane or a different class of anti-hypertensive agent should be considered.

Anaphylactoid reactions during low-density lipoprotein (LDL) apheresis

On rare occasions, patients receiving ACE inhibitors during apheresis of low-density lipoproteins (LDL) with dextran sulphate have suffered life-threatening anaphylactoid reactions. Such reactions were avoided by temporarily withholding the ACE inhibitor before each apheresis.

Densitisation

Patients who receive ACE inhibitors during desensitisation treatment (e.g. for bee or wasp stings) have suffered sustained anaphylactoid reactions; in the same patients these reactions were avoided when the ACE inhibitors were temporarily withheld, but reappeared with inadvertent re-administration of the medicinal product.

Hepatic failure

In very rare cases ACE inhibitors have been associated with a syndrome that begins with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death; however, the mechanism of this syndrome is not known. Patients who receive Bellisin tablets and who develop jaundice or significant hepatic enzyme elevation should stop taking the treatment and seek appropriate medical attention.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and with no other complications, neutropenia occurs occasionally. Neutropenia and agranulocytosis are reversible following withdrawal of the ACE inhibitor. Bellisin tablets should be used with great caution in patients with collagen vascular disease, immunosuppressive treatment, treatment with allopurinol or procainamide or a combination of these factors, especially if there is prior impairment of renal function. Some such patients may develop severe infections, which in rare cases do not respond to intensive antibiotic treatment. If Bellisin tablets are used in such patients, periodical monitoring of leucocyte counts is recommended and patients should be instructed to report any sign of infection.

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.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, Bellisin tablets may be less effective in reducing arterial pressure in black patients than in other patients, possibly because of a higher prevalence of low renin status in the black hypertensive population.

Cough

Cough has been reported with use of ACE inhibitors. Typically the cough is not productive, persistent and ceases when treatment is withdrawn. Cough induced by ACE inhibitors should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients who undergo major surgery or during anaesthesia with agents that cause hypotension, Bellisin tablets may block the formation of angiotensin II, secondary to compensatory renin release. If hypotension occurs and it is thought to be due to this mechanism, it may be corrected by volume expansion.

Hyperkalaemia

Elevation of serum potassium concentration has been observed in some patients treated with ACE inhibitors, including Bellisin tablets. Patients at risk of developing hyperkalaemia include those with renal insufficiency, diabetes mellitus or those simultaneously receiving potassium-sparing diuretics, potassium supplements or salt substitutes that contain potassium, or patients who are taking other drugs that are associated with an increase in serum potassium (e.g. heparin). If simultaneous use of the agents referred to above is considered appropriate, regular monitoring of serum potassium concentration is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral anti-diabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium

In general the combination of lithium and Bellisin tablets is not recommended (see section 4.5).

Pregnancy and lactation

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, 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).

Use in lisinopril is not recommended during breast-feeding

4.5 Interaction with other medicinal products and other forms of interaction

Antihypertensive agents

When Bellisin tablets are combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

The combination of lisinopril with aliskiren-containing medicines should be avoided (see sections 4.3 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 sections 4.3, 4.4 and 5.1).

Diuretics

When a diuretic is added to the treatment of a patient who is receiving Bellisin tablets, the anti-hypertensive effect is usually additive.

In patients receiving treatment with diuretics, and especially those in whom diuretic treatment has begun recently, an excessive decrease in arterial tension may occur when Bellisin tablets is administered concomitantly. The possibility of symptomatic hypotension with Bellisin tablets may be minimised by withdrawing the diuretic before administering Bellisin tablets (see section 4.4.).

Potassium supplements, potassium-sparing diuretics or salt substitutes containing potassium

Although in clinical studies serum potassium generally remained within normal limits, hyperkalaemia occurred in some patients. Risk factors for the development of hyperkalaemia are: renal insufficiency, diabetes mellitus and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or salt substitutes containing potassium; use of any of these, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If Bellisin tablets is administered with a potassium-losing diuretic, the hypokalaemia caused by the diuretic may be reduced.

Lithium

There have been reports of reversible increases in serum lithium concentrations and toxicity during simultaneous administration of lithium and ACE inhibitors. Simultaneous use of thiazide diuretics may increase the risk of lithium toxicity and potentiate the already increased toxicity of lithium with ACE inhibitors. Use of Bellisin tablets with lithium is not recommended, but if this combination is considered necessary serum lithium levels should be monitored carefully (see section 4.4.).

Non-steroidal anti-inflammatory drugs (NSAIs), including acetylsalicylic acid ≥ 3 g/day

Chronic administration of NSAIs may reduce the anti-hypertensive effect of an ACE inhibitor. NSAIs and ACE inhibitors have an additive effect on the increase in serum potassium and may cause a deterioration in renal function. Such effects are usually reversible. Acute renal insufficiency may occur on rare occasions, especially in patients with compromised renal function, such as older or dehydrated patients.

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be

very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Tricyclic antidepressants/Antipsychotic agents/Anaesthetics

Simultaneous use of certain anaesthetic drugs, tricyclic antidepressants and antipsychotic agents with ACE inhibitors may cause an additional decrease in arterial pressure (see section 4.4.).

Sympathomimetic agents

Sympathomimetic agents may reduce the anti-hypertensive effects of ACE inhibitors.

Anti-diabetic agents

Epidemiological studies have indicated that simultaneous use of ACE inhibitors and anti-diabetic drugs (insulins, oral anti-diabetic agents) may cause an increase in hypoglycaemic effect with a risk of hypoglycaemia. It appears that this phenomenon is more likely to occur during the first few weeks of combined treatment and in patients with renal impairment.

Acetyl salicylic acid, thrombolytic agents, beta blockers, nitrates

Bellisin tablets may be used together with acetyl salicylic acid (at cardiological doses), thrombolytic agents, beta blockers and/or nitrates.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, 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.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See 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. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Breastfeeding:

Because no information is available regarding the use of Bellisin tablets during breastfeeding, Bellisin is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

When driving or operating machinery, it should be borne in mind that feelings of dizziness or tiredness may occur occasionally.

4.8 Undesirable effects

The following adverse reactions have been observed and reported during treatment with Bellisin tablets and other ACE inhibitors, with the frequencies indicated below: Very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$), very rare ($< 1/10,000$) not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

rare: decreased haemoglobin, decreased haematocrit,
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

Metabolic and nutritional disorders:

very rare: hypoglycaemia

Nervous system and psychiatric system disorders :

Common: dizziness, headache
Uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disorders, hallucinations
rare: mental confusion, olfactory disturbance
frequency not known: depressive symptoms, syncope

Cardiac and vascular disorders:

Common: orthostatic effects (including hypotension)
Uncommon: myocardial infarct or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4.), palpitations, tachycardia, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

Common: cough
Uncommon: rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

Common: diarrhoea, vomiting
Uncommon: nausea, abdominal pain and indigestion
rare: dry mouth
very rare: pancreatitis, intestinal angiooedema, hepatitis (hepatocellular or cholestatic), jaundice and hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus,
rare: urticaria, alopecia, psoriasis, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4)
very rare: sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma

A symptomatic complex has been reported that may include one or more of the following situations: fever, vasculitis,

myalgia, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated red blood cells sedimentation rate (ESR), eosinophily and leucocytosis, skin rash, photosensitivity or other dermatological manifestations.

Renal and urinary disorders:

Common:	renal dysfunction
rare:	uraemia, acute renal insufficiency
very rare:	oliguria/anuria

Reproductive system and breast disorders:

Uncommon:	impotence
rare:	gynaecomastia

Endocrine disorders:

rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

General disorders and administration site conditions:

Uncommon:	fatigue, asthenia
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Investigations:

Uncommon	increased blood urea, increased serum creatinine, increased hepatic enzymes, hyperkalaemia
rare:	increased serum bilirubin, hyponatraemia

Safety data from clinical studies suggest that lisinopril is generally well tolerated in hypertensive paediatric patients, and that the safety profile in this age group is comparable to that seen in adults.

Reporting 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; e-mail: medsafety@hpra.ie

4.9 Overdose

There are limited data available on overdosage in humans. The symptoms associated with ACE inhibitor overdosage may be hypotension, circulatory shock, electrolytic changes, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

The recommended treatment for overdose is intravenous perfusion of physiological serum. If hypotension occurs the patient should be placed in the shock position. If available, treatment with a perfusion of intravenous angiotensin II and/or catecholamines may also be considered. If administration is recent, steps should be taken to eliminate Bellisin tablets (e.g. emesis, gastric lavage, administration of absorbent agents and sodium sulphate). Bellisin tablets may be removed from the general circulation by haemodialysis (see section 4.4.). In the event of bradycardia resistant to treatment, use of a pacemaker is indicated. Vital constants and serum electrolyte and creatinine concentrations should be checked frequently.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03.

Mechanism of action

Bellisin tablets is an inhibitor of peptidyl dipeptidase which inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide angiotensin II. Angiotensin II also stimulates secretion of aldosterone by the suprarenal cortex. Inhibition of ACE results in lower concentrations of angiotensin II, which leads to a reduction in vasopressor activity and decreased aldosterone secretion; the latter may cause an increase in serum potassium concentration.

Pharmacodynamic effects

Although it is thought that the mechanism by which lisinopril reduces arterial pressure is due principally to inhibition of the renin-angiotensin-aldosterone system, lisinopril has been shown to have an anti-hypertensive effect even in hypertensive patients with low renin levels. ACE is identical to kininase II, an enzyme that degrades bradykinin. It has not yet been determined whether elevated levels of bradykinin, a potent vasodilator peptide, play a role in the therapeutic effects of lisinopril.

Clinical efficacy and safety

The effect of Bellisin tablets on mortality and morbidity in cardiac insufficiency has been studied by comparing a high dose (32.5 mg or 35 mg once a day) with a low dose (2.5 mg or 5 mg once a day). In one study of 3164 patients, with median observation of surviving patients of 46 months, the high dose of Bellisin tablets resulted in a 12% decrease in the risk of the combined evaluation parameter of mortality and hospitalisation for any reason ($p=0.002$) and an 8% decrease in the risk of mortality due to all causes and cardiovascular hospitalisation ($p=0.036$), compared with the low dose.

Decreases in the risk of mortality due to all causes (8%, $p=0.128$) and cardiovascular mortality (10%; $p=0.073$) were observed. In a post hoc analysis, the number of hospital admissions for cardiac insufficiency was reduced by 24% ($p=0.002$) in patients treated with Bellisin tablets at high doses, compared with low doses. Beneficial effects were similar in patients treated with high doses and low doses of Bellisin tablets.

The study results showed that the overall adverse reaction profiles for patients treated with high or low doses of Bellisin tablets were similar both in nature and number. Foreseeable reactions resulting from ACE inhibition, such as hypotension or impaired renal function, were treatable and rarely prompted withdrawal of the treatment. Cough was less frequent in patients treated with high doses of Bellisin tablets than with low doses.

In the GISSI-3 clinical trial, in which a 2x2 factorial design was used to compare the effects of Bellisin tablets and nitroglycerin separately or in combination for six weeks versus a control in 19,394 patients to whom the treatment was administered within 24 hours of an acute myocardial infarction, Bellisin tablets produced a statistically significant decrease of 11% in the risk of mortality compared with the control ($2p=0.03$). The decrease in risk with nitroglycerin was not significant, but the combination of Bellisin tablets and that drug produced a significant decrease in the risk of mortality of 17% versus the control ($2p=0.02$). In the subgroups of older people (age > 70 years) and women, predefined as patients with a high risk of mortality, significant beneficial effects were observed in the combined evaluation parameter of mortality and cardiac function. The combined evaluation parameter in all patients, as well as in the high-risk subgroups, after six months also showed a beneficial effect in patients treated with Bellisin tablets or Bellisin tablets plus nitroglycerin for six weeks, which indicates a preventive effect of Bellisin tablets. As is to be expected with any vasodilator treatment, therapy with Bellisin tablets was associated with an increased incidence of hypotension and renal dysfunction, but the latter were not associated with a proportional increase in mortality.

In one multicentre, randomised, double-blind clinical trial which compared Bellisin tablets with a calcium antagonist in 335 hypertensive patients with Type 2 diabetes mellitus with incipient nephropathy characterised by microalbuminuria, administration of Bellisin tablets 10 mg to 20 mg once a day for 12 months reduced systolic and diastolic arterial pressure by 13/10 mmHg and urinary excretion of albumin by 40%. In comparison with the calcium antagonist, which produced a similar decrease in arterial pressure, the patients treated with Bellisin tablets displayed a significantly greater decrease in urinary albumin excretion, which provides a proof that Bellisin tablets's inhibitory action on ACE

reduces microalbuminuria by way of a direct mechanism on the renal tissues additional to its hypotensor effect.

Treatment with lisinopril does not affect glycaemic control, as shown by the absence of any significant effect on levels of glycosylated haemoglobin (HbA_{1c}).

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.

Paediatric population

In a clinical study involving 115 paediatric patients with hypertension, aged 6-16 years, patients who weighed less than 50 kg received either 0.625 mg, 2.5 mg or 20 mg of lisinopril once a day, and patients who weighed 50 kg or more received either 1.25 mg, 5 mg or 40 mg of lisinopril once a day. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with a consistent antihypertensive efficacy demonstrated at doses greater than 1.25 mg.

This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mm Hg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race.

5.2 Pharmacokinetic properties

Lisinopril is an orally active non sulph-hydrylic ACE inhibitor.

Absorption

After oral administration of lisinopril, peak serum concentrations are obtained in around seven hours, although there was a tendency for peak serum concentrations to be delayed slightly in patients with acute myocardial infarct. According to urinary recovery, mean absorption of lisinopril is 25%, with interpatient variability of 6-60% in the dosage range studied (5-80 mg). In patients with cardiac insufficiency, absolute bioavailability is reduced by approximately 16%. Absorption of lisinopril is unaffected by the presence of food.

Distribution

Lisinopril does not appear to bind to serum proteins other than angiotensin converting enzyme (ACE). Studies in rats indicate that lisinopril scarcely crosses the blood-brain barrier.

Elimination

Lisinopril does not undergo metabolism and is excreted unchanged in the urine. After multiple administration lisinopril displays an effective half-life of accumulation of 12.6 hours. Clearance of lisinopril in healthy patients is approximately 50 ml/min. The decrease in serum concentrations displays a prolonged terminal phase which does not contribute to accumulation of the drug. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment

Hepatic impairment in cirrhotic patients caused a decrease in absorption of lisinopril (around 30%, determined by urinary recovery) and an increase in exposure (around 50%) compared with healthy subjects because of a decrease in clearance.

Renal impairment

Renal impairment decreases elimination of lisinopril, which is excreted via the kidneys, although this decrease begins to be clinically significant only when the rate of glomerular filtration is lower than 30 ml/min. In slight to moderate renal impairment (creatinine clearance 30-80 ml/min.) mean AUC increased only by 13%, while in severe renal impairment (creatinine clearance 5-30 ml/min.) this value increased by a factor of 4.5.

Lisinopril may be eliminated by dialysis. Over four hours of haemodialysis, plasma lisinopril concentrations fell by an average of 60%, with clearance by dialysis of between 40 and 55 ml/min.

Heart failure

Patients with heart failure insufficiency have greater exposure to lisinopril than healthy individuals (mean increase in AUC 125%), although based on urinary recovery of this drug, there is a decrease in absorption of around 16% compared with said group of healthy individuals

Older people

Older people have higher blood concentrations and higher values for area under the curve of concentration against time (increase of around 60%) in comparison with young individuals.

Paediatric population

The pharmacokinetic profile of lisinopril was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73m². After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours, and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults.

AUC and C_{max} values in children in this study were consistent with those observed in adults.

5.3 Preclinical safety data

Pre-clinical data do not show any special risks to humans according to conventional studies of general pharmacology, repeat-dose toxicity, genotoxicity and carcinogenic potential. It has been shown that angiotensin converting enzyme inhibitors, as a class, have adverse effects on late foetal development that cause foetal death and congenital defects, especially in the cranium. There have also been reports of foetotoxicity, retarded intrauterine growth and patent ductus arteriosus. It is thought that these developmental abnormalities are due in part to the direct action of ACE inhibitors on the foetal renin-angiotensin system and in part to the ischaemia caused by maternal hypotension and the decrease in the foetal-placental blood flow and in the supply of oxygen/nutrients to the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Calcium hydrogen phosphate anhydrous
Maize starch
Pregelatinised starch (maize)
Magnesium stearate
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Blister strip comprising of clear transparent PVC film (coated uniformly with PVdC on the inner side) with a backing of aluminium foil (coated with heat seal lacquer). The tablets are available in pack sizes of 14, 28, 30, 50, 56, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Ltd
Spafield
Cork Road
Cashel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0408/057/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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