

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellisin 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg lisinopril (as lisinopril dihydrate).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Product imported from the UK:

Light peach coloured, capsule shaped, biconvex uncoated tablets debossed with '2' 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

Cardiac insufficiency

Treatment of symptomatic cardiac insufficiency

Acute myocardial infarct

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

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes 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.

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 may have volume and/or salt depletion. 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 shown 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 to arterial pressure response.

Dosage may be increased until arterial pressure is controlled or up to a maximum of 40 mg daily.

Heart Failure

In patients with symptomatic heart failure, Bellisin tablets should be used as adjuvant treatment to diuretics and, where appropriate, digitalic agents or betablockers. 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).

Acute myocardial infarct

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 infarct)

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 infarct 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 use

The safety and efficacy of use in children have not been fully demonstrated. Use at paediatric age is therefore not recommended.

Use in the elderly

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 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)

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 cardiac insufficiency, 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 cardiopathy or cerebrovascular disease in whom an excessive decrease in arterial pressure could cause myocardial infarct or stroke.

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 for subsequent doses, which may usually be administered without difficulty, as arterial pressure increases following volume expansion.

In some patients with cardiac insufficiency 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 infarct

Treatment with Bellisin tablets should not be started in patients with acute myocardial infarct 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 infarct 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.

Aortal and mitral valve stenosis/hypertrophic myocardiopathy

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

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 insufficiency, 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 infarct, 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 other 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 withdrawing the ACE inhibitor before each apheresis.

Densensitisation

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 withdrawn, but reappeared with inadvertent readministration of the pharmaceutical specialty.

Hepatic insufficiency

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 is used in such patients, periodical monitoring of leucocyte counts is recommended and patients should be instructed to report any sign of infection.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angiooedema in patients of black race than in other patients.

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

Cough

Cough has been reported with use of ACE inhibitors. Typically the cough is not productive or 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

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).

4.5 Interaction with other medicinal products and other forms of interaction

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 elderly or dehydrated patients.

Other anti-hypertensive agents

Simultaneous use of such agents may increase the hypotensive effects of Bellisin tablets. Concomitant use with nitroglycerin and other nitrates or other vasodilator agents may lower arterial pressure yet further.

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).

Lactation

Because no information is available regarding the use of Lisinopril during breastfeeding, Lisinopril 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 fatigue 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 frequent ($\geq 10\%$), frequent ($\geq 1\%$, $< 10\%$), infrequent ($\geq 0.1\%$, $< 1\%$), rare ($\geq 0.01\%$, $< 0.1\%$), very rare ($< 0.01\%$) including reports of isolated cases.

Disorders of the blood and lymphatic system:

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 problems:

very rare:	Hypoglycaemia
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Nervous system disorders and psychiatric problems:

frequent:	dizziness, headache
infrequent:	mood swings, paraesthesia, vertigo, palate changes, sleep disorders.
rare:	mental confusion

Cardiac and vascular problems:

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

Respiratory, thoracic and mediastinal problems:

frequent: cough.
 infrequent: rhinitis.
 very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.

Digestive problems:

frequent: diarrhoea, vomiting.
 infrequent: nausea, abdominal pain and indigestion
 rare: mouth dryness
 very rare: pancreatitis, intestinal angiooedema, hepatitis (hepatocellular or cholestatic), jaundice.

Disorders of the skin and subcutaneous tissue:

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

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 erythrocyte sedimentation rate (ESR), eosinophily and leucocytosis, skin rash, photosensitivity or other dermatological manifestations.

Renal and urinary problems:

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

Disorders of the reproductive system and breast:

infrequent: impotence.
 rare: Gynaecomastia.

General problems and problems at site of administration:

infrequent: fatigue, asthenia.

Laboratory tests:

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

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 insufficiency, 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. induction of vomiting, 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.

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.

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.

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 infarct, 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 elderly patients (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}).

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.

Cardiac insufficiency

Patients with cardiac 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.

Elderly patients

Elderly patients 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.

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)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Blister packs of 28 tablets contained in an overlabelled outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

WPR Healthcare Ltd
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA565/47/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2011

10 DATE OF REVISION OF THE TEXT