SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cosyrel 10 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 10 mg of bisoprolol fumarate (equivalent to 8.49 mg bisoprolol) and 10 mg of perindopril arginine (equivalent to 6.790 mg perindopril).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink beige, oblong, bilayer film-coated tablet of 10 mm length and 5.7 mm width, engraved with ' ' on one face and '10/10' on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cosyrel is indicated as substitution therapy for treatment of hypertension and/or stable coronary artery disease (in patients with a history of myocardial infarction and/or revascularisation) in adult patients adequately controlled with bisoprolol and perindopril given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

The usual posology is one tablet once daily.
Patients should be stabilized with bisoprolol and perindopril at the same dose level for at least 4 weeks. The fixed dose combination is not suitable for initial therapy.

If a change of posology is required, titration should be done with the individual components.

Special population

Renal impairment (see section 4.4 and 5.2)
Cosyrel 10 mg/10 mg is not suitable for patients with renal impairment. In these patients, an individual dose titration with the monocomponents is recommended.

Hepatic impairment (see section 4.4 and 5.2)
No dosage adjustment is necessary in patients with hepatic impairment.

Elderly
Cosyrel should be administered according to the renal function.

Paediatric population
The safety and efficacy of Cosyrel in children and adolescents have not been established. No data are available. Therefore, use in children and adolescents is not recommended.

Method of administration

Cosyrel tablet should be taken as a single dose once daily in the morning before a meal.

4.3 Contraindications

- Hypersensitivity to the active substances, or to any of the excipients listed in section 6.1, or to any other angiotensin converting enzyme (ACE) inhibitor
- Acute heart failure or during episodes of heart failure decompensation requiring *i.v.* inotropic therapy
- Cardiogenic shock
- Second or third degree AV block (without pacemaker)
- Sick sinus syndrome
- Sinoatrial block
- Symptomatic bradycardia
- Symptomatic hypotension
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- Untreated phaeochromocytoma (see section 4.4)
- Metabolic acidosis
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Concomitant use of Cosyrel with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m²) (see sections 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

All warnings and precautions for use related to each component are applicable to Cosyrel.

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or gradual discontinuation of treatment, using the individual components, may be necessary.

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Cosyrel should promptly be discontinued. Therapy with beta-blocker must be continued. Appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly.

This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Race:
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough:
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor induced cough should be considered as part of the differential diagnosis of cough.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Combination with lithium:
The combination of lithium and perindopril is generally not recommended (see section 4.5).

Combination with potassium sparingdrugs, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing drugs, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 4.5).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.