SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

Cosyrel 5 mg/5 mg film-coated tablets.

Cosyrel 5 mg/10 mg film-coated tablets.

Cosyrel 10 mg/5 mg film-coated tablets.

Cosyrel 10 mg/10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cosyrel 5 mg/5 mg One film-coated tablet contains 5 mg of bisoprolol fumarate (equivalent to 4,24 mg bisoprolol) and 5 mg of perindopril arginine (equivalent to 3,395 mg perindopril).

Cosyrel 5 mg/10 mg One film-coated tablet contains 5 mg of bisoprolol fumarate (equivalent to 4,24 mg bisoprolol) and 10 mg of perindopril arginine (equivalent to 6,790 mg perindopril).

Cosyrel 10 mg/5 mg One film-coated tablet contains 10 mg of bisoprolol fumarate (equivalent to 8,49 mg bisoprolol) and 5 mg of perindopril arginine (equivalent to 3,395 mg perindopril).

Cosyrel 10 mg/10 mg 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.

Cosyrel 5 mg/5 mg Pink beige, oblong, bilayer scored film-coated tablet of 8,3 mm length and 4,5 mm width, engraved with '  ' on one face and '5/5' on the other face.

Cosyrel 5 mg/5 mg scored tablet can be divided into equal doses.

Cosyrel 5 mg/10 mg Pink beige, oblong, bilayer scored film-coated tablet of 9,8 mm length and 5,4 mm width, engraved with '  ' on one face and '5/10' on the other face.

Cosyrel 5 mg/10 mg scored tablet can be divided into equal doses.

Cosyrel 10 mg/5 mg Pink beige, round, bilayer film-coated tablet with a diameter of 7 mm and a curvature radius of 12,7 mm, engraved with '  ' on one face and '10/5' on the other face.

Cosyrel 10 mg/10 mg 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) and/or stable chronic heart failure with reduced systolic left ventricular function 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 stabilised with bisoprolol and perindopril at the same dose level for at least 4 weeks. The fixed dose combination is not suitable for initial therapy.

For patients stabilised with bisoprolol 2,5 mg and perindopril 2,5 mg can use one half 5 mg/5 mg tablet once daily.

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

Special populations

Renal impairment (see section 4.4 and 5.2)

Cosyrel 5/5 mg

In patients with renal impairment, the recommended dose of **Cosyrel 5/5 mg** should be based on creatinine clearance as outlined in table 1 below.

Table 1 dosage adjustment in renal impairment.

Creatinine clearance (ml/min)	**Recommended daily dose**
$Cl_{CR} \geq 60$	One tablet of Cosyrel 5/5 mg
$30 < Cl_{CR} < 60$	One half tablet of Cosyrel 5/5 mg
$Cl_{CR} < 30$	Not suitable. Individual dose titration with the monocomponents is recommended

Cosyrel 5/10 mg

In patients with renal impairment, the recommended dose of **Cosyrel 5/10 mg** should be based on creatinine clearance as outlined in table 2 below.

Table 2 dosage adjustment in renal impairment.

Creatinine clearance (ml/min)	**Recommended daily dose**
$Cl_{CR} \geq 60$	One half tablet of Cosyrel 5/10 mg
$Cl_{CR} < 60$	Not suitable. Individual dose titration with the monocomponents is recommended

Cosyrel 10/5 mg

In patients with renal impairment, the recommended dose of **Cosyrel 10/5 mg** should be based on creatinine clearance as outlined in table 3 below.

Table 3 dosage adjustment in renal impairment.

Creatinine clearance (ml/min)	**Recommended daily dose**
$Cl_{CR} \geq 60$	One tablet of Cosyrel 10/5 mg
$Cl_{CR} < 60$	Not suitable. Individual dose titration with the monocomponents is recommended

Cosyrel 10/10 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 (patients ≥ 65 years of age)

Cosyrel should be administered according to the renal function.

Paediatric population

The safety and efficacy of **Cosyrel** in children and adolescents less than 18 years of age, have not been established. No data are available. Therefore, **Cosyrel** should not be used in children and adolescents.

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 (< 50 bpm).
- 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.
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs) These patients must never again be given these medicines (see section 4.4).
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney (see section 4.4).
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy Concomitant administration with **Cosyrel** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (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).
- Concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5).

- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- Concomitant use of fluoroquinolones with ACE-inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **Cosyrel**, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine. (see sections 4.3 and 4.6).

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 has been reported 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, once the blood pressure has increased after volume expansion.

In 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 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 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 (epinephrine) 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 in patients treated with ACE-inhibitors such as contained in **Cosyrel**. 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.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE-inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Hepatic failure

ACE-inhibitors such as contained in **Cosyrel** 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 such as contained in **Cosyrel** cause a higher rate of angioedema in black patients than in non-black patients.

ACE-inhibitors, including 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 such as contained in **Cosyrel**. 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 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 medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). 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 dysrhythmias. If concomitant use of the above-mentioned medicines 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 contraindicated (see section 4.3).

Combination with potassium sparing medicines, potassium supplements or potassium-containing salt substitutes.

The combination of perindopril and potassium sparing medicines, potassium supplements or potassium-containing salt substitutes is 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).

Cosyrel should not be used concomitantly with aliskiren (see section 4.3).

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.

Concomitant use of fluoroquinolones

Concomitant use of fluoroquinolones and ACE-inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal

impairment and elderly patients. (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE-inhibitors/Angiotensin receptor blockers whether used separately and/or concomitantly.

Combination with calcium antagonists, Class I antidysrhythmic medicines and centrally acting antihypertensive medicines

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antidysrhythmic medicines and with centrally acting antihypertensive medicines is not recommended see section 4.5).

Stopping treatment

Abrupt cessation of therapy with a beta-blocker such as contained in **Cosyrel** should be avoided, especially in patients with ischaemic heart disease, because this may lead to transitional worsening of heart condition. The posology should be decreased gradually, using the individual components, ideally over a period of two weeks while at the same time starting the replacement therapy if necessary.

Bradycardia

If, during treatment, resting heart rate drops below 50 - 55 beats per minute and the patient experiences symptoms related to bradycardia, **Cosyrel** dose should be downtitrated using the individual components with an appropriate dose of bisoprolol.

First degree AV block

Given their negative dromotropic effect, beta-blockers such as contained in **Cosyrel** should be administered with caution to patients with first degree AV block.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

ACE-inhibitors, such as perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Prinzmetal's angina

Beta-blockers such as contained in **Cosyrel** may increase the number and the duration of angina episodes in patients with Prinzmetal's angina. The use of selective blockers of beta-1 adrenergic receptors is possible in mild cases and only in combination with vasodilators.

Renal impairment

In case of renal impairment, the daily dose of Cosyrel should be adjusted according to creatinine clearance (see section 4.2). Routine monitoring of potassium and creatinine are part of medical practice for these patients (see section 4.8).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE-inhibitors may lead to further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE-inhibitors, increases in blood urea and serum creatinine,

have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is present there is an increased risk of severe hypotension and renal insufficiency and **Cosyrel** should not be used (see section 4.3). Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitors such as contained in **Cosyrel** (see section 4.3). Treatment with diuretics may

be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Kidney transplantation

There is no experience regarding the administration of perindopril arginine as contained in **Cosyrel** in patients with recent kidney transplantation.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE-inhibitor such as contained in **Cosyrel**. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Patients receiving ACE-inhibitors, such as contained in **Cosyrel** during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation

Patients receiving ACE-inhibitors such as contained in **Cosyrel** during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE-inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Beta-blockers, such as bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactoid reactions. Epinephrine (adrenaline) treatment does not always yield the expected therapeutic effect.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors such as contained in **Cosyrel.** Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such

patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Bronchospasm (Bronchial asthma,obstructive airways diseases)

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. An increase of the airway resistance may occur when beta-blockers such as contained in **Cosyrel,** are used in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

Diabetic patients

Caution is advised when Cosyrel is used in patients with diabetes mellitus with large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked by beta-blockers.

Strict fasting

Caution is advised in patients with strict fasting.

Peripheral arterial occlusive disease

Aggravation of symptoms may occur with beta-blockers such as contained in **Cosyrel**, especially when starting therapy.

Anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of dysrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist must be aware of beta-blockade because of the potential for interactions with other medicines, resulting in brady dysrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought

necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Psoriasis

Patients with psoriasis or with a history of psoriasis should not be given beta-blockers such as contained in **Cosyrel.**

Phaeochromocytoma

In patients with known or suspected to have phaeochromocytoma bisoprolol should always be given in combination with an alpha-receptor blocker.

Thyrotoxicosis (hyperthyroidism)

The symptoms of hyperthyroidism may be masked by bisoprolol such as contained in **Cosyrel.**

Primary aldosteronism

Patients with primary hyperaldosteronism will not respond to anti-hypertensive medication acting through inhibition of the renin-angiotensin system. Therefore, the use of **Cosyrel** is not recommended.

Heart failure

There is no therapeutic experience with **Cosyrel** containing bisoprolol in the treatment of heart failure in patients with the following diseases and conditions;

- insulin dependent diabetes mellitus (type I),
- severely impaired renal function,

- severely impaired hepatic function,
- restrictive cardiomyopathy,
- congenital heart disease,
- haemodynamically significant organic valvular disease,
- myocardial infarction within the last 3 months.

Excipients

Level of sodium

Cosyrel contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between bisoprolol and perindopril have been observed in an interaction study conducted in healthy volunteers. Only information on interactions with other medicines that are known for the individual active substances is provided below.

Medicines inducing hyperkalaemia

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia such as aliskiren, potassium salts, potassium-sparing diuretics, ACE-inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant medicines such as ciclosporin or tacrolimus, trimethoprim. The combination of these medicines increases the risk of hyperkalaemia.

Concomitant use contraindicated (see section 4.3)

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE-inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Aliskiren

The concomitant therapy with **Cosyrel** and aliskiren is contra-indicated in diabetic or impaired renal patients, due to the risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe

anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/Valsartan

The concomitant use of perindopril as contained in **Cosyrel** with sacubitril/valsartan is contraindicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see section 4.3 and 4.4).

Concomitant use not recommended

Linked to bisoprolol

Centrally acting antihypertensives such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine).

Concomitant use of centrally acting antihypertensives may worsen heart failure by lowering the central sympathetic tonus (reduced heart rate and cardiac output, vasodilation). Abrupt termination, particularly before down-titration of beta-blocker therapy, may increase the risk of rebound hypertension.

Class I antidysrhythmic medicines (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone)

The effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect be increased.

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type have a negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Linked to perindopril

Aliskiren

In patients without diabetes or impaired renal function, the risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality are increased.

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker

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).

Patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening of renal function (including acute renal failure) as compared to the use of a single renin-angiotensin-aldosterone system inhibitor medicine. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

Estramustine

There is a risk of increased adverse effects such as angioneurotic oedema (angioedema).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Potassium sparing diuretics (e.g. triamterene, amiloride...), potassium (salts)

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).

The combination of **Cosyrel** which contains perindopril with the above-mentioned medicines is not recommended (see section 4.4). If concomitant use is nonetheless indicated they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium

Lithium toxicity has been reported during concomitant administration of lithium with ACE-inhibitors. Use of perindopril with lithium is contraindicated (see section 4.3).

Concomitant use which require special care

Linked to bisoprolol and perindopril as contained in Cosyrel

Antidiabetic medicines (insulins, oral hypoglycaemic agents)

Concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Concomitant administration of bisoprolol with insulin and oral antidiabetic medicines may increase blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) (including aspirin ≥ 3 g/day)

The administration of Cosyrel simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may attenuate the antihypertensive effect of bisoprolol and perindopril.

In addition, concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of deterioration of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Antihypertensive medicines and vasodilators

Concomitant use with antihypertensive medicines, vasodilators (such as nitroglycerin, other nitrates or other vasodilators) or with other medications which have a blood-pressure-reducing potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotensive effects of perindopril and bisoprolol.

Tricyclic antidepressants/Antipsychotics/Anaesthetics

Concomitant use of ACE-inhibitors as contained in **Cosyrel** with certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics may result in further reduction of blood pressure.

Concomitant use of bisoprolol as contained in **Cosyrel** with anaesthesics may lead to reduced reflex tachycardia and increased risk of hypotension.

Sympathomimetics

Beta-sympathomimetics (e.g. isoprenaline, dobutamine) combination with bisoprolol may reduce the effects of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine) combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents, leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.

Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors.

Linked to bisoprolol as contained in Cosyrel

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine

Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antidysrhythmic medicines (e.g. amiodarone).

Effect on atrio-ventricular conduction time may be potentiated.

Parasympathomimetic medicines

Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Concomitant use of topical beta-blockers (e.g. eye drops for glaucoma treatment), may add to the systemic effects of bisoprolol.

Digoxin Reduction of heart rate, increase of atrio-ventricular conduction time.

Linked to perindopril as contained in Cosyrel

Baclofen

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE-inhibitor such as contained in **Cosyrel**. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

In arterial hypertension, when prior diuretic therapy have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE-inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure, the ACE-inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

When eplerenone or spironolactone are used at doses between 12,5 mg to 50 mg per day in combination with low doses of ACE-inhibitors as treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, (and previously treated with ACE-inhibitors and loop diuretics), the risk of hyperkalaemia, which may be fatal, is increased, especially when not adhering to the prescribing recommendations on this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

A close monitoring of the kalaemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Racecadotril

ACE-inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be increased when used concomitantly with racecadotril (a medicine used against acute diarrhoea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Combination use to be taken into consideration

Linked to bisoprolol as contained in Cosyrel

Mefloquine

There is an increased risk of bradycardia if used with mefloquine.

Monoamine oxidase inhibitors (except MAO-B inhibitors)

The hypotensive effect of the beta-blockers is enhanced and there is a risk to develop hypertensive crisis.

Linked to perindopril as contained in Cosyrel

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin)

Gliptins decrease the activity of dipeptidyl peptidase IV (DPP-IV), which increases the risk of angioedema in patients co-treated with an ACE-inhibitor.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE-inhibitor therapy including perindopril.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **Cosyrel** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take Cosyrel during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which

have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Cosyrel should be stopped immediately and alternative therapy should be started.

Bisoprolol

Bisoprolol should not be used in pregnancy (see section 4.3). It has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn (reduce placental perfusion associated with growth retardation, intrauterine death, abortion or early labour and adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant.

The risk of hypoglycaemia and bradycardia is present for 3 days after the birth of the baby.

Perindopril

Perindopril should not be used in pregnancy (see section 4.3). Foetal exposure to ACE-inhibitors such as perindopril during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations. **Cosyrel** passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria (renal failure) in new-borns, have been reported after administration of **Cosyrel** during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Breastfeeding

Cosyrel should not be used by women breastfeeding their babies (see section 4.3).

It is not known whether bisoprolol is excreted in human milk. Because no information is available regarding the use of perindopril during breastfeeding, alternative treatments with better established safety profiles during breastfeeding should be used.

Fertility

There are no clinical data on fertility with the use of **Cosyrel.**

4.7 Effects on ability to drive and use machines

Cosyrel may influence the ability to drive and use machines. Patients should not drive and use machines until they know how **Cosyrel** affects them. Hypotension, dizziness and visual disturbances have been reported with **Cosyrel.**

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions to bisoprolol include headache, dizziness, worsening of heart failure, hypotension, cold extremities, nausea, vomiting, abdominal pain, diarrhoea, constipation, asthenia and fatigue.

The most common adverse reactions reported in clinical trials and observed with perindopril include headache, dizziness, vertigo, paraesthesia, visual disturbance, tinnitus, hypotension, cough, dyspnoea, nausea, vomiting, abdominal pain, diarrhoea, constipation, dysgeusia, dyspepsia, rash, pruritus, muscle cramps and asthenia.

List of adverse reactions reported during clinical trials

The following undesirable effects have been observed during clinical trials use with bisoprolol or perindopril given separately and ranked under the MedDRA classification by body system and under the following frequency.

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

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Bisoprolol	**Perindopril**
Infections and infestations	Rhinitis	Rare	Very rare
Blood and lymphatic System Disorders	Agranulocytosis (see section 4.4)	-	Very rare
	Pancytopenia	-	Very rare
	Leukopenia	-	Very rare
	Neutropenia (see section 4.4)	-	Very rare
	Thrombocytopenia (see section 4.4)	-	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH	-	Very rare
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	Rare
Psychiatric disorders	Mood altered	-	Uncommon
	Sleep disorder	Uncommon	Uncommon
	Depression	Uncommon	Uncommon*
	Nightmares, Hallucinations	Rare	-
	Confusion	-	Very rare
Nervous system disorders	Headache**	Common	Common
	Dizziness**	Common	Common
	Vertigo	-	Common
	Dysgeusia	-	Common
	Paraesthesia	-	Common
Eye disorders	Visual impairment	-	Common

	Reduced tear flow (to be considered if the patient uses lenses)	Rare	-
	Conjunctivitis	Very rare	-
Ear and labyrinth disorders	Tinnitus	-	Common
	Hearing disorders	Rare	-
Cardiac disorders	Bradycardia	Very common	-
	Worsening of heart failure	Common	-
	AV-conduction disturbances	Uncommon	-
	Dysrthymia	-	Very rare
	Angina pectoris	-	Very rare
	Myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
Vascular disorders	Hypotension and effects related to hypotension	Common	Common
	Feeling of coldness or numbness in the extremities	Common	-
	Orthostatic hypotension	Uncommon	-
	Flushing	-	Rare*
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
Respiratory, thoracic and mediastinal disorders	Cough	-	Common
	Dyspnoea	-	Common
	Bronchospasm	Uncommon	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal disorders	Abdominal pain	Common	Common
	Constipation	Common	Common

	Diarrhoea	Common	Common
	Nausea	Common	Common
	Vomiting	Common	Common
	Dyspepsia	-	Common
	Dry mouth	-	Uncommon
	Pancreatitis	-	Very rare
Hepato-biliary disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Rare	Very rare
Skin and subcutaneous tissue disorders	Rash	-	Common
	Pruritus	-	Common
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	-	Uncommon
	Urticaria	-	Uncommon
	Hyperhidrosis	-	Uncommon
	Hypersensitivity reactions (itching, flush, rash)	Rare	-
	Erythema multiform	-	Very rare
	Alopecia	Very rare	-
	Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash	Very rare	-
Musculoskeletal and connective tissue disorders	Muscle cramps	Uncommon	Common
	Muscular weakness	Uncommon	-
Renal and urinary disorders	Renal insufficiency	-	Uncommon
	Acute renal failure	-	Rare
	Anuria/Oliguria	-	Rare*

Reproductive system and breast disorders	Erectile dysfunction	-	Uncommon
	Potency disorders	Rare	-
General disorders and administration site conditions	Asthenia	Common	Common
	Fatigue	Common	-
Investigations	Hepatic enzyme increased	Rare	Rare
	Blood bilirubin increased	-	Rare
	Increased triglycerides	Rare	-
	Haemoglobin decreased and haematocrit decreased (see section 4.4)	-	Very rare

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

**These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1 - 2 weeks.

The following adverse events were reported from post marketing experience

MedDRA System Organ Class	**Undesirable Effects**
Blood and lymphatic system disorders	Eosinophilia
Metabolism and nutrition disorders	Hypoglycaemia (see sections 4.4 and 4.5), Hyperkalaemia, reversible on discontinuation, Hyponatraemia
Nervous system disorders	Somnolence, Syncope
Cardiac disorders	Palpitations, Tachycardia
Vascular disorders	Vasculitis, Raynaud's phenomenon
Skin and subcutaneous tissue disorders	Photosensitivity reactions, Pemphigoid, Psoriasis aggravation

Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia
General disorders and administration site conditions	Chest pain, Malaise, Peripheral oedema, Pyrexia
Investigations	Blood urea increased, Blood creatinine increased
Injury, poisoning and procedural complications	Fall

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, undesirable effects can be precipitated and /or of increased severity (see section 4.8).

Bisoprolol

Symptoms

The most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

Management

If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on

the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another medicine with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic medicines and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Perindopril

Symptoms

Symptoms associated with overdosage of ACE-inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Management

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0,9 %) solution. If hypotension occurs, the patient should be placed in the shock position (patient to lie on their back with legs elevated). If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group ACE-inhibitors, other combinations. ATC code C09BX02.

Mechanism of action

Bisoprolol

Bisoprolol is a beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

Perindopril

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (ACE). The converting enzyme, or kininase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to

the blood pressure-lowering action of ACE-inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Pharmacodynamic effects

Bisoprolol

Bisoprolol has no significant negative inotropic effects.

Bisoprolol reaches its maximum effects 3 - 4 hours after administration. Due to the half-life of 10 - 12 hours, bisoprolol acts for 24 hours.

The maximum blood-pressure-lowering effects of bisoprolol are generally reached after 2 weeks.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. The decrease in plasma renin activity is proposed as a mechanism of action underlying the antihypertensive effect of beta-blockers.

Bisoprolol reduces the sympatho-adrenergic response by blocking cardiac beta-adrenergic receptors. This results in a decrease in heart rate and contractility, causing a reduction in oxygen consumption by the myocardium, which is the desired effect in the case of angina associated with underlying coronary heart disease.

Perindopril

Hypertension

Perindopril is active in all grades of hypertension mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases , while the glomerular filtration rate (GFR) is usually unchanged.

Heart failure

Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Clinical efficacy and safety

Bisoprolol

A clinical study in patients with stable symptomatic systolic heart failure (83 % NYHA class III and 17 % NYHA IV) (ejection fraction < 35 %). the total mortality was reduced from 17,3 % to 11,8 % (relative reduction 34%). A decrease in sudden death (3,6 % vs 6,3 %, relative reduction 44 %) and a reduced number of heart failure episodes requiring hospital admission (12 % vs 17,6 %, relative reduction 36 %) was observed with also a significant improvement of the NYHA functional status. The hospital admissions during the initiation and titration phase with bisoprolol, were due to bradycardia (0,53 %), hypotension (0,23 %), and acute decompensation (4,97 %) which were not more frequent than in the placebo-group (0 %, 0,3 % and 6,74 %). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

A clinical study over 24 months in patients aged ≥ 65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤ 35 %, who had not been treated previously with ACE-inhibitors, beta-blockers, or angiotensin receptor blockers. revealed a trend towards a higher frequency of deterioration of chronic heart failure when bisoprolol was used as the initial 6 months treatment compared to enalapril as the initial 6 months treatment. However, irrespective of whether bisoprolol or enalapril was used for the initial 6 months of combination therapy with bisoprolol + enalapril, at study end the result showed a similar rate of the primary combined endpoint death and hospitalisations d (32,4 % in the bisoprolol-first group vs. 33,1 % in the enalapril-first group, per-protocol population).

Perindopril

Hypertension

Perindopril is active in all grades of hypertension mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases , while the GFR is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours trough effects are about 87 - 100 % of peak effects.

In responding patients, the maximum antihypertensive effect is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

Perindopril has vasodilatory properties. It improves large artery elasticity and decreases the media lumen ratio of small arteries.

An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE-inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure

Studies in patients with heart failure have demonstrated

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

Administration of 2,5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

A clinical study where the primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20 %, 95 % CI [9,4; 28,6] – p < 0,001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2,2 % corresponding to a RRR of 22,4 % (95 % CI [12,.0; 31,6] – p < 0,001) in the primary endpoint was observed by comparison to placebo.

In a subgroup of patients treated with beta-blockers the addition of perindopril to beta-blockers showed a significant absolute reduction of 2,2 % (relative risk reduction of 24 %, 95 % CI [9,5; 36,4]) compared to beta-blockers without perindopril in the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data

Clinical studies have shown no significant beneficial effect of dual blockade therapy 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.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

A study designed to test the benefit of adding aliskiren to therapy with an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both, was terminated early because 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

No data are available with **Cosyrel** in children and adolescents less than 18 years of age.

5.2 Pharmacokinetic properties

The rate and extent of absorption of bisoprolol and perindopril from Cosyrel are not significantly different, respectively, from the rate and extent of absorption of bisoprolol and perindopril when taken alone as monotherapy.

Bisoprolol

Absorption

Bisoprolol is almost completely (> 90 %) absorbed from the gastrointestinal tract and, because of its small hepatic first-pass metabolism (approximately 10 %), it has a bioavailability of approximately 90 % after oral administration.

Distribution

The distribution volume is 3,5 l/kg. The plasma protein binding of bisoprolol is about 30 %.

Biotransformation and elimination

Bisoprolol is excreted from the body by two routes. 50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50 % is excreted by the kidneys in an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10 - 12 hours gives a 24 hour effect after dosing once daily.

Special populations

The kinetics of bisoprolol are linear and independent of age.

Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The

pharmacokinetics in patients with chronic heart failure and with impaired liver or renal function has not been studied. In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64 ± 21 ng/ml at a daily dose of 10 mg and the half-life is 17 ± 5 hours.

Perindopril

Absorption

After oral administration, perindopril is well absorbed and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Distribution

The volume of distribution is approximately 0,2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20 %, principally to ACE, but is concentration-dependent.

Biotransformation

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril

yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Elimination

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Linearity

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Special populations

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Bisoprolol

Preclinical data did not reveal genotoxicity or carcinogenicity.

For reproduction toxicology see section 4.6.

Perindopril

Preclinical data did not reveal mutagenicity or carcinogenicity.

For reproduction toxicology see section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Cellulose microcrystalline PH 102 (E460)

Calcium carbonate (E170)

Pregelatinized maize starch

Sodium starch glycolate type A (E468)

Silica colloidal anhydrous (E551)

Magnesium stearate (E572)

Croscarmellose sodium (E468)

Film-coating

Glycerol (E422)

Hypromellose (E464)

Macrogol 6 000

Magnesium stearate (E572)

Titanium dioxide (E171)

Iron dioxide yellow (E172)

Iron dioxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 30 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

6.5 Nature and contents of container

Tablet container of 30 film-coated tablets white polypropylene tablet container equipped with a low-density polyethylene flow reducer and a white opaque stopper containing a desiccant gel.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Servier Laboratories SA (Pty) Ltd

Building Number 4

Country Club Estate

21 Woodlands Drive

Woodmead, 2191

8. REGISTRATION NUMBERS

Cosyrel 5 mg/5 mg: 51/7.1.3/0495

Cosyrel 5 mg/10 mg: 51/7.1.3/0496

Cosyrel 10 mg/5 mg: 51/7.1.3/0497

Cosyrel 10 mg/10 mg: 51/7.1.3/0498

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 May 2021

10. DATE OF REVISION OF TEXT

1 August 2022