PRODUCT INFORMATION

NAME OF THE DRUG

COVERSYL® 2.5MG
Perindopril arginine 2.5mg

COVERSYL® 5MG
Perindopril arginine 5mg

COVERSYL® 10MG
Perindopril arginine 10mg

DESCRIPTION

COVERSYL is perindopril arginine which has the chemical name, L-arginine (2S, 3aS, 7aS) - 1 - N - [(S) -1 - ethoxycarbonyl butyl ] - L - alanyl perhydroindole-2 - carboxylate (code name S9490-6). Perindopril is a dipeptide monoacid monoester with a perhydroindole group and no sulphhydryl radical. Perindopril arginine is a white powder, readily soluble in purified water, slightly soluble in 95% ethanol and practically insoluble in chloroform. Perindopril has five asymmetric centres. The drug is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

CAS Registry Number: 612548-45-5

Molecular formula: C₁₉H₃₂N₂O₅, C₆H₁₄N₄O₂

Chemical structure:

Exciipients:
Lactose, magnesium stearate, maltodextrin, silica - colloidal anhydrous, sodium starch glycollate (type A), macrogol 6000. All tablet coatings also include glycerol, hypromellose and titanium dioxide.

Specific to:
- COVERSYL 5MG - premix for light-green colour coating [copper chlorophyllin (E141ii)]
- COVERSYL 10MG - premix for green colour coating [copper chlorophyllin (E141ii)]
**PHARMACOLOGY**

**Mechanism of Action**

Perindopril (prodrug), following hydrolysis to perindoprilat, inhibits angiotensin converting enzyme (ACE) both in vitro and in vivo. It is thought that ACE inhibitors reduce blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increased plasma renin activity and a decrease in aldosterone. In addition to its effects on circulating ACE, COVERSYL binds to and inhibits tissue converting enzyme, predominantly in the kidney and vascular wall. The contribution of this mechanism to the overall antihypertensive effect of COVERSYL is unknown. Animal studies have demonstrated reversal of vascular hypertrophy and an improvement in the ratio of elastin to collagen in the vessel wall. Studies in man have demonstrated an improvement in the visco-elastic properties of large vessels and in compliance. Studies in animals and humans suggest that specific and competitive suppression of the renin-angiotensin-aldosterone system is the main mechanism by which blood pressure is reduced. However, antihypertensive activity has also been observed in patients with low renin activity. COVERSYL may also inhibit the degradation of the potent vasodepressor peptide, bradykinin, and this action may contribute to its antihypertensive action. COVERSYL appears to reduce peripheral resistance and may influence arterial compliance.

**Pharmacokinetics and Metabolism**

Following oral administration, COVERSYL is rapidly absorbed with bioavailability of 24%. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1 hour. Bioavailability of the active metabolite perindoprilat is approximately 27%. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of COVERSYL. Protein binding of perindoprilat is 20%, principally to angiotensin converting enzyme. Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The terminal half-life of the unbound fraction is approximately 17 hours. When COVERSYL is administered chronically, steady state of perindoprilat is reached within 4 days, and perindoprilat does not accumulate. Food intake may reduce hepatic biotransformation to perindoprilat. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure (see **DOSAGE AND ADMINISTRATION**). Apart from perindoprilat, the administration of perindopril leads to the formation of 5 other metabolites, all of which are inactive and exist in very low quantities. One of these is the glucurononoconjugate of perindoprilat, which is formed by a hepatic first-pass effect. This effect does not appear to have any influence on the kinetics of perindoprilat.

**Pharmacodynamics**

Studies carried out in animal models of hypertension have shown that COVERSYL is a specific competitive angiotensin I converting enzyme inhibitor. The administration of COVERSYL to patients with essential hypertension results in a reduction in supine and standing blood pressure without any significant effect on heart rate. Abrupt withdrawal of COVERSYL has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak inhibition of ACE activity and peak reduction in blood pressure occurs 4-6 hours after administration. The durations of these effects are dose related and at the recommended dose range, both effects have been shown to be maintained over a 24-hour period.

In haemodynamic studies carried out in animal models of hypertension, blood pressure reduction after COVERSYL administration was accompanied by a reduction in peripheral arterial resistance and improved arterial wall compliance. In studies carried out in patients with essential hypertension the reduction in blood pressure was accompanied by a reduction in peripheral resistance with no change, or a small increase in renal blood flow and no change in glomerular filtration rate. An increase in the compliance of large arteries was also observed. When COVERSYL is administered together with a thiazide-type diuretic, the antihypertensive activity of COVERSYL may be potentiated in some patients, and this effect is evident after four weeks of
treatment. COVERSYL, like other ACE inhibitors, may compensate for thiazide-induced hypokalaemia.

In one study of 48 patients where low-dose perindopril equivalent to COVERSYL® 2.5MG was compared with correspondingly low doses of enalapril (2.5 mg) or captopril (6.25 mg) in patients with congestive heart failure, significantly different blood pressure responses were noted. Blood pressure fell significantly with captopril and enalapril following the first dose. However, whilst perindopril inhibited plasma ACE comparably with enalapril, the blood pressure changes were insignificant and similar to placebo for up to 10 hours of regular observation. The possibility of late hypotensive response cannot be ruled out with perindopril.

**CLINICAL TRIALS**

**Patients with stable coronary artery disease:**

The effects of perindopril were compared to placebo in patients with stable coronary artery disease with no clinical signs of heart failure. The EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting 4 years. 12218 patients aged over 18 were randomised: 6110 patients to high dose perindopril, equivalent to COVERSYL 10MG and 6108 patients to placebo.

The primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction, and/or cardiac arrest with successful resuscitation.

The trial population had evidence of coronary artery disease documented by previous myocardial infarction at least 3 months before screening, coronary revascularisation at least 6 months before screening, angiographic evidence of stenosis (at least 70% narrowing of one or more major coronary arteries), or positive stress test in men with a history of chest pain.

Study medication was added to conventional therapy, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on doses of perindopril equivalent to COVERSYL 2.5MG or COVERSYL 5MG for 2 weeks, and then titrated up to a dose of perindopril equivalent to COVERSYL 10MG during the 2 following weeks. A dose of perindopril equivalent to COVERSYL 10MG was then maintained for the whole duration of the study. If this dose was not well tolerated, it could be reduced to a dose of perindopril equivalent to COVERSYL 5MG once daily.

Most of the patients also received platelet inhibitors, lipid-lowering agents and beta-blockers. At the end of the study, the proportions of patients on these concomitant medications were 91%, 69% and 63% respectively.

The results of the EUROPA study, specifically the primary endpoint and its components (cardiovascular mortality, non-fatal myocardial infarction or resuscitated cardiac arrest) for the intention-to-treat (ITT) population are presented in Table 1.
### Table 1 - EUROPA study results (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Perindopril (N=6110)</th>
<th>Placebo (N=6108)</th>
<th>Absolute Risk Reduction [95% CI]</th>
<th>NNT <strong>Note 2</strong> over 4.2yr trial period (per year)</th>
<th>Relative Risk Reduction [95% CI]</th>
<th>P (log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events (Primary composite endpoint)</td>
<td>488 (8.0%)</td>
<td>603 (9.9%)</td>
<td>1.9% [0.87; 2.90]</td>
<td>54 (227)</td>
<td>20% [9; 29]</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Primary endpoint component:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Cardiovascular mortality</td>
<td>215 (3.5%)</td>
<td>249 (4.1%)</td>
<td>non-significant</td>
<td>-</td>
<td>14% [-3; 28]</td>
<td>0.107</td>
</tr>
<tr>
<td>- Non-fatal MI <strong>Note 3</strong></td>
<td>295 (4.8%)</td>
<td>378 (6.2%)</td>
<td>1.4% [0.55; 2.17]</td>
<td>74 (311)</td>
<td>22% [10; 33]</td>
<td>0.001</td>
</tr>
<tr>
<td>- Cardiac arrest with successful resuscitation</td>
<td>6 (0.1%)</td>
<td>11 (0.2%)</td>
<td>non-significant</td>
<td>-</td>
<td>46% [-47; 80]</td>
<td>0.223</td>
</tr>
<tr>
<td><strong>Secondary endpoints:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total mortality</td>
<td>375 (6.1%)</td>
<td>420 (6.9%)</td>
<td>non-significant</td>
<td>-</td>
<td>11% [-2; 23]</td>
<td>0.101</td>
</tr>
<tr>
<td>Non-fatal and fatal MI</td>
<td>320 (5.2%)</td>
<td>418 (6.8%)</td>
<td>1.6% [0.76; 2.44]</td>
<td>63 (265)</td>
<td>23.9% [12, 34]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Notes:**
1. The EUROPA study was designed to have adequate statistical power to detect a treatment effect on the composite primary endpoint, and not for the individual components
2. NNT = Number of patients needed to be treated to prevent one event
3. MI = Myocardial Infarction

The reduction in the primary composite endpoint was mainly due to a reduction in the number of non-fatal myocardial infarctions. There was no significant reduction in the rate of cardiovascular mortality or total mortality in patients taking perindopril compared to those taking placebo.

After a mean follow-up of 4.2 years, treatment with a dose of perindopril equivalent to COVERSYL 10MG once daily resulted in a significant relative risk reduction of 20% (95%CI: 9-29) in the primary combined endpoint: 488 patients (8.0%) reported events in the perindopril group compared to 603 patients (9.9%) in the placebo group (p = 0.0003). Improvements in the primary composite endpoint achieved statistical significance after 3 years of continuous treatment on perindopril.

**INDICATIONS**

COVERSYL is indicated for:
- The treatment of hypertension;
- The treatment of heart failure. In such patients it is recommended that COVERSYL be given with a diuretic and/or digoxin under close medical supervision. (The safety and efficacy of COVERSYL has not been demonstrated for New York Heart Association Category IV patients); and
- Patients with established coronary artery disease (see Clinical Trials) who are stable on concomitant therapy and have no heart failure, to reduce the risk of non-fatal myocardial infarction or cardiac arrest.
CONTRAINDICATIONS

COVERSYL is contraindicated:

- in patients with a history of previous hypersensitivity to the active ingredient perindopril or any of the excipient ingredients present in COVERSYL;
- during pregnancy and for lactating women;
- in patients with bilateral or unilateral renal artery stenosis;
- in patients with a history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous ACE-inhibitor treatment; and
- in patients haemodialysed using high-flux polyacrylonitrile (“AN69”) membranes who are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (eg. cuprophane or polysulphone PSF).

PRECAUTIONS

Hyperkalaemia

Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, increases in serum potassium have been observed in some patients treated with ACE inhibitors including perindopril. Risk factors for the development of hyperkalaemia 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). 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 INTERACTIONS WITH OTHER MEDICINES). In some patients hyponatraemia may co-exist with hyperkalaemia. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. It is recommended that serum electrolytes (including sodium potassium and urea) should be measured from time to time when ACE inhibitors are given, especially when diuretics are also prescribed.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see INTERACTIONS WITH OTHER MEDICINES).

Lithium

The combination of lithium and perindopril is generally not recommended (see INTERACTIONS WITH OTHER MEDICINES).

Potassium sparing drugs, 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 INTERACTIONS WITH OTHER MEDICINES).
Angio-oedema

Patients with a history of angio-oedema unrelated to ACE inhibitor therapy may be at increased risk of angio-oedema while receiving an ACE inhibitor.

Life-threatening angio-oedema has been reported with most ACE inhibitors. The overall incidence is approximately 0.1-0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angio-oedema is non-pitting oedema of the skin mucous membrane and subcutaneous tissue.

Angio-oedema of the face, extremities, lips, tongue, mucous membranes, glottis and/or larynx has been reported in patients treated with ACE inhibitors and has been reported uncommonly with COVERSYL (see ADVERSE EFFECTS). This may occur at any time during therapy. In such cases COVERSYL should be promptly discontinued and the patient carefully observed until the swelling disappears.

Where such cases have been described with other ACE inhibitors and swelling has been confined to the face and lips, the condition has generally resolved without treatment although antihistamines have been useful in relieving symptoms. Angio-oedema associated with laryngeal oedema may be fatal or near fatal. In most cases symptoms occurred during the first week of treatment and the incidence appears to be similar in both sexes or those with heart failure or hypertension.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy (e.g. adrenaline and oxygen) should be given promptly. Treatment of progressive angio-oedema should be aggressive and failing a rapid response to medical therapy, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation.

Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

The onset of angio-oedema associated with use of ACE inhibitors may be delayed for weeks or months.

Patients may have multiple episodes of angio-oedema with long symptom-free intervals.

Angio-oedema may occur with or without urticaria.

Intestinal angio-oedema 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 angio-oedema 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.

There are reports when changing a patient to another ACE inhibitor was followed by recurrence of angio-oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angio-oedema, to a drug of this class (see CONTRAINDICATIONS). Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Anaphylactoid reactions during low-density lipoproteins (LD) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (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.
Anaphylactic reactions during desensitisation

Patients receiving ACE inhibitors 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.

Hypotension

Hypotension has been reported in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of COVERSYL use in severely salt/volume-depleted patients with impaired renal function, those treated vigorously with diuretics, after severe diarrhoea or patients on dialysis (see PRECAUTIONS and ADVERSE REACTIONS). Administration of a dose of perindopril equivalent to COVERSYL 2.5MG to patients with mild-moderate heart failure was not associated with any significant reduction in blood pressure.

In patients with severe congestive heart failure, with or without associated renal impairment, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of COVERSYL and/or diuretic is increased. In all high-risk patients it is advisable to initiate treatment with one COVERSYL 2.5MG tablet.

If hypotension occurs the patient should be placed in a supine position and if necessary infused with normal saline. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty when blood pressure has increased following volume expansion.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on RAAS activity, treatment with ACE inhibitors may be associated with oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea, nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of ACE inhibitor treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney, or bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.
If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine, which are usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION). Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see ADVERSE EFFECTS). If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory drug.

Perindopril is dialysable with a clearance of 70mL/min.

Kidney transplantation

There is no experience regarding the administration of COVERSYL in patients with a recent kidney transplantation.

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 ADVERSE EFFECTS).

Impaired Hepatic Function

Biotransformation of perindopril to perindoprilat mainly occurs in the liver. Studies in patients with impaired hepatic function have shown that kinetic parameters of perindopril were not modified by hepatic failure. With the exception of bioavailability, which was increased, kinetic parameters of perindopril (including $T_{\text{max}}$) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (see PHARMACOLOGY - Pharmacokinetics). The administration of perindopril leads to the formation of a glucurononoconjugate derivative of perindoprilat by a hepatic first-pass effect. The kinetic parameters of perindoprilat glucuronide are not modified by hepatic failure. The small changes in the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure.

Ethnicity

ACE inhibitors cause a higher rate of angioedema in patients of indigenous African origin than in patients of other racial origin. As with other ACE inhibitors, perindopril may be less effective in
lowering blood pressure in people of indigenous African origin than in people of other racial origin, possibly because of a higher prevalence of low-renin states in this population. It is unknown if the same observations have been made in patients of indigenous Australian origin.

Cough

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a class-effect of ACE inhibitor therapy with the incidence of cough varying between 2-15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins, which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Proteinuria

COVERSYL treatment has occasionally been associated with mild or transient proteinuria (<1 gram/per 24 hours). However in the majority of patients with pre-existing proteinuria treated with COVERSYL, proteinuria disappeared or remained stable. ACE inhibitors have a real potential to delay the progression of nephropathy in diabetic as well as hypertensive patients.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. COVERSYL 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 COVERSYL 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).

Dermatological Reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc). A causal relationship is difficult to assess.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Taste Disturbances (dysgeusia)

Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data are scarce and difficult to interpret.
Taste disturbances with ACE inhibitors have been described as suppression of taste or a metallic sensation in the mouth. Any dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within 1-3 months.

Agents Causing Renin Release

The effects of perindopril may be enhanced by concomitant administration of antihypertensive agents which cause renin release.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an angiotensin II receptor antagonist to an ACE-inhibitor) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Surgery and Anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. The treatment should be discontinued one day prior to the surgery. If perioperative hypotension occurs, volume expansion would be required.

Aortic or mitral valve Stenosis / hypertrophic cardiomyopathy

There has been some concern on theoretical grounds that patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or with hypertrophic cardiomyopathy might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

Stable coronary artery disease

If an episode of unstable angina pectoris, regardless of severity, occurs during the first month of perindopril treatment, a careful appraisal of the benefits/risks of continuing treatment should be performed.

Lactose intolerance

COVERSYL tablets contain lactose. Patients with an intolerance to lactose, rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric Use

Use of COVERSYL in children is not recommended as no data establishing safety or effectiveness in children are available.
Use in Elderly Patients

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing COVERSYL to elderly patients. The initial dose in the elderly should always be one COVERSYL 2.5MG tablet daily and patients should be monitored closely during the initial stages of treatment (see DOSAGE AND ADMINISTRATION).

In a study of 91 elderly patients with a mean age of 71.9 years, a 6% increase in serum potassium occurred in the first month of treatment and subsequently remained stable. There was no change in the group in blood urea, creatinine or creatinine clearance.

Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.

Use in Pregnancy: Category D

The use of ACE inhibitors is contra-indicated during pregnancy (see CONTRAINDICATIONS).

As with all ACE inhibitors, COVERSYL should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with COVERSYL and avoided during the treatment. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data, however, show that ACE inhibitors cross the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure in utero may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death in utero.

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.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to ACE inhibitors during the first trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal and neonatal toxicity hypotension, hyperkalaemia, renal failure, skull hypoplasia, oligohydramnios and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure or to the mother's underlying disease.

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalaemia. Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. If such complications
arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion. While small amounts of perindopril are found in the breast milk of animals, there is no human data.

**Use in Lactation**

Animal studies have shown that perindopril and its metabolites are excreted in milk during lactation, but there are no human data. It is therefore recommended that COVERSYL should not be given to lactating women as the possible effect on the newborn is unknown. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Carcinogenicity**

Carcinogenicity studies have not been conducted with perindopril arginine. No evidence of carcinogenic activity was observed in mice and rats when perindopril erbumine was administered via drinking water at levels up to 7.5mg/kg/day for 2 years.

**Mutagenesis**

At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign. Results from a broad set of assays for gene mutation and chromosomal damage with perindopril arginine suggest no genotoxic potential at clinical doses.

**Impairment of Fertility**

The effects of perindopril arginine on fertility have not been investigated. Studies in rats showed no impairment of male or female fertility at oral perindopril erbumine doses up to 10mg/kg/day.

**Interactions with other medicines**

**Lithium**

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination is necessary, careful monitoring of serum lithium levels should be performed (see PRECAUTIONS).

**Diuretics**

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuation of the diuretic and/or ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. The starting dose of the ACE-inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

**Combination use of ACE inhibitors, anti-inflammatory drugs and thiazide diuretics**

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases
the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

**Gold**

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

**Agents affecting serum potassium**

The ACE inhibitor class can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril, the concomitant use of an ACE inhibitor with a potassium-sparing diuretic (e.g. spironolactone, triamterene, or amiloride), immunosuppressant (e.g. cyclosporin), angiotensin receptor blocker, potassium supplements, or potassium-containing salt substitute can increase the risk of hyperkalaemia, therefore the combination of perindopril with the above mentioned drugs is not recommended (see **PRECAUTIONS**). If co-administration is indicated they should be used with caution and the patient's serum potassium monitored frequently.

**Antihypertensive agents and vasodilators**

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

**Antidiabetic agents (eg. insulin, hypoglycaemic sulphonylureas)**

Reported with captopril and enalapril. The use of ACE inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonylureas. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements) and appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

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

Drugs with prostaglandin synthetase inhibitor properties (e.g. indomethacin) or non-steroidal anti-inflammatory drug (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, non-selective NSAIDs or COX-2 inhibitor), may diminish the antihypertensive efficacy of concomitantly-administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between COVERSYL or indomethacin or other non-steroidal anti-inflammatory drugs.

The administration of a non-steroidal anti-inflammatory drug may lead to an increased risk of worsening 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.

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**

Perindopril may be used concomitantly with thrombolytics, acetylsalicylic acid (when used as a thrombolytic), beta-blockers and/or nitrates.
Tetracycline and other drugs that interact with magnesium

The simultaneous administration of tetracycline with an ACE inhibitor may significantly reduce the absorption of tetracycline, possibly due to the magnesium content in the ACE inhibitor tablets. This interaction should be considered if co-prescribing an ACE inhibitor and tetracycline or other drugs that interact with magnesium.

Agents Affecting Sympathetic Activity

As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with concomitant administration of a drug with sympathetic activity and COVERSYL. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors

Tricyclic antidepressants/Antipsychotics/Anaesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see PRECAUTIONS).

Effects on the Ability to Drive and Operate Machinery

The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery, especially at the start of treatment or when changing over from other preparations, or during concomitant use of alcohol.

Effects on laboratory tests

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

ADVERSE REACTIONS

Adverse events that have been observed during treatment with perindopril are listed below ranked under the following frequency: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000 and including isolated reports).

Psychiatric disorders:
Uncommon: mood or sleep disturbances (insomnia, dream abnormality)

Nervous system disorders:
Common: headache, dizziness, drowsiness, vertigo, paresthesia
Very rare: depression, confusion, hallucinations

Ear/labyrinth and Eye disorders:
Common: tinnitus, vision disturbance

Cardiac disorders:
Common: palpitations
Very rare: arrhythmia, angina pectoris and myocardial infarction and stroke - possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), vasculitis

Vascular disorders:
Common: hypotension and effects related to hypotension, flushing, impaired peripheral circulation
Very rare: stroke - possibly secondary to excessive hypotension in high risk patients (see
PRECAUTIONS), vasculitis

Respiratory, thoracic and mediastinal disorders:
Common: cough, dyspnoea, epistaxis, discomfort on exertion
Uncommon: bronchospasm
Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:
Common: nausea, vomiting, abdominal pain, dysgeusia, diarrhoea, dyspepsia, constipation
Uncommon: dry mouth
Very rare: pancreatitis

Hepato-biliary disorders:
Very rare: hepatitis, either cytolytic or cholestatic (see PRECAUTIONS)

Skin and subcutaneous tissue disorders:
Common: rash, pruritus
Uncommon: urticaria, angio-oedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see PRECAUTIONS)
Very rare: erythema multiform

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Uncommon: renal insufficiency
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence

General disorders and Administration site conditions:
Common: asthenia
Uncommon: sweating, atypical chest pain

Blood and the lymphatic system disorders:
Very rare: Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. An unexplained change in prothrombin ratio was reported in one patient. Haemolytic anaemia has been reported in patients with congenital G-6PDH deficiency (see PRECAUTIONS).

Investigations:
Rare: serum bilirubin elevation, liver enzyme elevation

Withdrawals
In total 56 of 1275 patients studied (4.4%) stopped treatment because of adverse reactions. In a specific study of 632 patients in which 36 (5.7%) patients withdrew because of adverse events, a plausible or probable relationship with COVERSYL treatment was considered to exist in 19 (3%) cases.

Post marketing experience (frequency unknown)

Blood and the lymphatic system disorders: Eosinophilia.

Metabolism and nutrition disorders: hypoglycaemia (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES), hyperkalaemia reversible on discontinuation (see PRECAUTIONS), hyponatraemia.

Nervous system disorders: somnolence, syncope

Cardiac disorders: tachycardia,

Skin and subcutaneous tissue disorders: eczema, photosensitivity reactions
Musculoskeletal, connective tissue and bone disorders: arthralgia, myalgia
General disorders and Administration site condition: malaise, oedema peripheral, pyrexia
Investigations: increases in blood urea and serum creatinine
Injury, poisoning and procedural complications: fall

DOSAGE AND ADMINISTRATION

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. Whilst this effect has not been shown to be clinically significant, it is recommended that COVERSYL should be taken before meals.

Renal Impairment

In patients with renal failure, treatment should begin with one COVERSYL 2.5MG tablet daily. Dosage should be adjusted as indicated below according to creatinine clearance. Creatinine and potassium levels should be closely monitored.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between 30 and 60</td>
<td>one COVERSYL 2.5MG tablet daily</td>
</tr>
<tr>
<td>Between 15 and 30</td>
<td>one COVERSYL 2.5MG tablet every 2 days</td>
</tr>
<tr>
<td>Below 15</td>
<td>one COVERSYL 2.5MG tablet on day of dialysis [Perindopril is dialysable (70 mL/min)].</td>
</tr>
</tbody>
</table>

Hypertension

The usual starting dose is one COVERSYL 5MG tablet once daily, taken in the morning. Optimum control of blood pressure is achieved by increasing the dose, titrating it against the blood pressure to a maximum of one COVERSYL® 10MG tablet once daily.

A starting dose of one COVERSYL 2.5MG tablet per day is recommended in the following patients who may be at risk of ACE inhibitor-induced hypotension:

- **Combination with a Diuretic**
  The administration of COVERSYL to patients under current diuretic therapy may induce hypotension and sometimes, but more rarely, acute renal failure, at the beginning of the treatment. It is recommended to monitor plasma creatinine during the first month of treatment.

- **Elderly Hypertensives**
  Elderly hypertensive patients should start treatment with one COVERSYL 2.5MG tablet daily, with titration to one COVERSYL 5MG tablet if necessary. It is recommended that renal function be assessed before starting treatment.

- **Other patients who may be at risk of ACE inhibitor-induced hypotension**
  Patients with renovascular hypertension, salt and/or volume depletion, or cardiac decompensation may have a strongly activated renin-angiotensin-aldosterone system. These patients may experience an excessive drop in blood pressure following the first dose of an ACE inhibitor.

Congestive Heart Failure

Treatment of congestive heart failure with COVERSYL should be initiated under close medical supervision.
The usual starting dose of COVERSYL is one COVERSYL 2.5MG tablet once daily, which should be given with a diuretic and/or digitalis. This is increased to one COVERSYL 5MG tablet once daily for maintenance.

Patients with severe hepatic or renal impairment and/or severe salt/volume depletion are particularly sensitive to ACE inhibitors. Doses in these patients should be carefully titrated as no pharmacokinetic and dose titration studies have been conducted.

**Reduction of risk of cardiovascular events**

In patients with stable coronary artery disease, COVERSYL should be introduced at a dose of one COVERSYL 5MG tablet once daily for two weeks, and then increased to one COVERSYL 10MG tablet once daily, depending on tolerance and renal function.

Elderly patients should receive one COVERSYL 2.5MG tablet once daily for one week, then one COVERSYL 5MG tablet once daily the next week, before increasing the dose up to one COVERSYL 10MG tablet once daily depending on tolerance and renal function (see table under DOSAGE AND ADMINISTRATION - Renal impairment).

**OVERDOSAGE**

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see PRECAUTIONS section). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.

**PRESENTATION AND STORAGE CONDITIONS**

**COVERSYL 2.5MG:** White, round, convex, film-coated tablets containing 2.5mg of perindopril arginine.

**COVERSYL® 5MG:** Light-green, rod-shaped, film-coated tablets engraved with the Servier logo on one face and scored on both edges containing 5mg of perindopril arginine.

**COVERSYL® 10MG:** Green, round, biconvex film-coated tablets containing 10mg of perindopril arginine with a logo on one face and the Servier logo on the other face.

Thirty (30) tablets supplied in a white HDPE bottle equipped with a white induction-sealed child resistant-closure and desiccant canisters/sachets.

Store in a dry place below 30°C. Shelf-life when stored as recommended: 3 years

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# A 10- tablet presentation is also available for medical sample or hospital pharmacy use
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POISONS SCHEDULE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
8 June, 2005

DATE OF MOST RECENT AMENDMENT
11 July, 2012