PRODUCT INFORMATION

NAME OF THE DRUG

COVERSYL PLUS 5MG/1.25MG  
Perindopril arginine 5mg / Indapamide hemihydrate 1.25mg

COVERSYL PLUS LD 2.5MG/0.625MG  
Perindopril arginine 2.5mg / Indapamide hemihydrate 0.625mg

DESCRIPTION

Active Ingredients

Perindopril is a dipeptide monoacid monoester with a perhydroindole group and no sulphhydryl radical. The drug substance is the arginine salt of perindopril. It has the chemical name, L-arginine (2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butyl]amino] propanoyl] octahydro-1H-indole-2-carboxylate (code name S9490-6). 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 : C\textsubscript{19}H\textsubscript{32}N\textsubscript{2}O\textsubscript{5}, C\textsubscript{6}H\textsubscript{14}N\textsubscript{4}O\textsubscript{2}

Chemical structure :

Indapamide is a non-thiazide indole derivative of chlorosulphonamide; chemical name 4-chloro-N-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-3-sulphamoylbenzamide hemihydrate. Indapamide is a white crystalline lipophilic powder, soluble in methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene, and practically insoluble in water.

CAS Registry Number : 26807-65-8

Molecular formula : C\textsubscript{16}H\textsubscript{16}ClN\textsubscript{3}O\textsubscript{3}S, \(\frac{1}{2}\) H\textsubscript{2}O
Chemical structure:

![Chemical structure](image)

Excipients

Lactose, magnesium stearate, silica - colloidal anhydrous, maltodextrin, sodium starch glycollate type A, macrogol 6000, glycerol, hypromellose, titanium dioxide.

PHARMACOLOGY

Pharmacological Mechanism of Action

COVERSYL PLUS is a combination of perindopril arginine, an angiotensin converting enzyme (ACE) inhibitor, and indapamide, a chlorosulphamoyl diuretic, in which the doses of the ACE inhibitor and diuretic components are lower than the usual doses used for monotherapy. Its pharmacological properties are derived from each of its components, in addition to those due to the synergistic action of the two products when combined on vascular endothelium and the target-organs of hypertension, with:

- an increase in vasorelaxation and a reduction in vasoconstriction, which are endothelium-dependent;
- a regression in renal effects (glomerulosclerosis, proteinuria), myocardial effects (left ventricular hypertrophy) and a reduction in capillary density.

COVERSYL PLUS exerts a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing in hypertensive patients regardless of age. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no associated effects. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergistic nature when compared with each of the products administered alone.

The combination of perindopril with indapamide is justified in the treatment of hypertension due to its action on several pathophysiological mechanisms, and due to the lessening of counter-regulatory mechanisms by one or other of the two components:

- indapamide reduces the vascular response to angiotensin II by depleting the cell of sodium and of calcium, whilst perindopril opposes the stimulation of the renin-angiotensin system (RAS) and the sympathetic nervous system induced by indapamide;
- the stimulation of the RAS caused by indapamide is blocked by perindopril;
- the potassium depletion linked to indapamide is compensated by the potassium-sparing effect of perindopril.

COVERSYL PLUS does not adversely affect lipid metabolism (total cholesterol, HDL and LDL cholesterol, triglycerides) or carbohydrate metabolism, even in hypertensive patients with diabetes.

Pharmacology of Perindopril

Perindopril (prodrug) following hydrolysis to perindoprilat, inhibits 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, perindopril 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 perindopril 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 humans 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. Perindopril may also inhibit the degradation of the potent vasodepressor peptide, bradykinin, and this action may contribute to its antihypertensive action. Perindopril appears to reduce peripheral resistance and may influence arterial compliance.

Studies carried out in animal models of hypertension have shown that perindopril is a specific competitive angiotensin I converting enzyme inhibitor. The administration of perindopril 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 perindopril has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak initiation of ACE activity and peak reduction in blood pressure occurs 4-6 hours after administration of perindopril. The duration 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 perindopril 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 perindopril is administered together with a thiazide-type diuretic, the antihypertensive activity of perindopril may be potentiated in some patients, and this effect is evident after four weeks of treatment. Perindopril, like other ACE inhibitors, may compensate thiazide-induced hypokalaemia.

**Pharmacology of Indapamide**

Indapamide is an oral antihypertensive agent. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated; both vascular and renal actions have been implicated.

The renal effects of indapamide are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity to functionally anephric patients lends support to the hypothesis.

The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on potassium or uric acid excretion. Only at doses greater than 2.5mg/day, i.e. at a dose of indapamide double that in one COVERSYL PLUS 5MG/1.25MG tablet and four times that in one COVERSYL PLUS LD 2.5MG/0.625MG tablet, is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies.

Indapamide does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

**Preclinical Safety Data**

Perindopril displays the typical effects of ACE inhibitors. In the rat, the target organ is the kidney; perindopril causes anatomical modifications in arteries which result in intrarenal haemodynamic
changes and an increase in blood urea and creatinine levels. The highest doses of indapamide administered by the oral route in different animal species manifested as an exacerbation of the diuretic properties of indapamide. The main symptoms in acute toxicity studies with indapamide administered by the intravenous or intraperitoneal routes are related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilatation.

In animal models, the combination of perindopril and indapamide has greater toxicity than that of the individual components. Renal manifestations of the effects of perindopril in the rat are increased when the drug is given in combination with indapamide (about 3 times the effect of perindopril alone). Renal impairment, resulting from loss of functional nephrons and irreversible renal fibrosis, is observed when perindopril is given in combination with indapamide in the rat. The combination of perindopril and indapamide produced gastrointestinal toxicity (haemorrhage, erosion and necrosis) in dogs, but similar effects were not observed in dogs with much higher doses of the individual components. The mechanism underlying perindopril/indapamide-induced gastrointestinal toxicity in dogs is unknown and the clinical relevance of this finding is questionable. In addition, the toxic effects of perindopril/indapamide in pregnant rats and rabbits are increased when compared to the effects of the drugs individually.

**Pharmacokinetics**

**Pharmacokinetics of COVERSYL PLUS**

The co-administration of perindopril and indapamide does not change the pharmacokinetic properties of the components administered separately.

**Pharmacokinetics of COVERSYL PLUS 5MG/1.25MG**

In three studies investigating the pharmacokinetics of perindopril and indapamide given either alone or in combination at doses equivalent to COVERSYL PLUS 5MG/1.25MG, the following pharmacokinetic parameters were obtained for the individual components:

<table>
<thead>
<tr>
<th>Dose form, active ingredient</th>
<th>Plasma C\textsubscript{max} (ng/mL)</th>
<th>Plasma AUC (ng/mL.h)</th>
<th>Plasma T\textsubscript{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril tablet</td>
<td>26 ± 3.2 [range 21-32]</td>
<td>34 ± 6.9 [range 26-46]</td>
<td>0.74 [range 0.5-1.1]</td>
</tr>
<tr>
<td>Indapamide capsule</td>
<td>15 ± 3.7 [range 9.7-24]</td>
<td>298 ± 79 [range 194-466]</td>
<td>2.0 [range 1.5-6.0]</td>
</tr>
<tr>
<td>Combination tablet:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-perindopril</td>
<td>33 ± 12 [range 11-73]</td>
<td>40 ± 10 [range 26-70]</td>
<td>0.75 [range 0.5-2.0]</td>
</tr>
<tr>
<td>-indapamide</td>
<td>16 ± 3.9 [range 9-24]</td>
<td>287 ± 64 [range 161-441]</td>
<td>1.5 [range 0.75-6.0]</td>
</tr>
</tbody>
</table>
Pharmacokinetics of COVERSYL PLUS LD 2.5MG/0.625MG

In a study investigating the pharmacokinetics of a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG in elderly and very elderly hypertensive patients (N=36), the following pharmacokinetic parameters were obtained for the individual active components:

<table>
<thead>
<tr>
<th>Indapamide</th>
<th>Perindoprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>25 ± 13</td>
</tr>
<tr>
<td>Plasma AUC (ng/mL.h)</td>
<td>366 ± 207</td>
</tr>
<tr>
<td>Plasma T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.5 ± 1.1</td>
</tr>
</tbody>
</table>

Pharmacokinetics of Perindopril

Following oral administration, perindopril is rapidly absorbed with bioavailability of 24%. Elimination is rapid, with excretion 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 perindopril. Protein binding of perindoprilat is 20%, principally to angiotensin converting enzyme (ACE). 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 perindopril 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, and hence its bioavailability. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac or 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.

Pharmacokinetics of Indapamide

Possibly related to its high lipid solubility, absorption of indapamide from the gastrointestinal tract is rapid (within 0.5 to 1 hour after an oral dose) and complete.

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80%) and, more specifically, to carbonic acid anhydrase (98%) without having any inhibiting activity on this enzyme. In plasma, it is relatively highly bound to plasma proteins (79%). It is also taken up to a significant degree in the vascular compartment, the drug has a relatively low apparent volume of distribution (approximately 60L) and 40% of the dose is located in the blood one hour after administration.

The decrease in plasma concentrations of unchanged indapamide is biphasic with terminal half lives between 14 and 25 hours. Both single and multiple dose data indicate that indapamide’s kinetics are linear. Steady state plasma levels are reached within three to four days after starting treatment and the drug does not accumulate in hypertensive patients with various degrees of renal insufficiency. Indapamide is extensively metabolised in the liver, mainly by CYP2C9 and CYP3A4 isozymes and by cytosolic hydrolysis enzymes. Care should be taken when administering indapamide in combination with drugs that alter the activity of these enzymes (see also Interactions with other medicines under PRECAUTIONS).

Following radioactivity studies using carbon-14, the main route of elimination is the urine, but only 5 to 7% of the dose is excreted into the urine as unchanged drug; 20 to 23% of total radioactivity is eliminated into the faeces. Renal clearance of indapamide (as unchanged drug) is approximately 5mL/minute, representing less than 10% of systemic clearance. The high lipid solubility of the indoline moiety confers to indapamide its highly localised binding to structures in the cardiovascular system.
INDICATIONS

COVERSYL PLUS 5MG/1.25MG
Treatment of hypertension. Treatment should not be initiated with this combination.

COVERSYL PLUS LD 2.5MG/0.625MG
Treatment of hypertension.

CONTRAINDICATIONS

COVERSYL PLUS 5MG/1.25MG and COVERSYL PLUS LD 2.5MG/0.625MG are contraindicated:

- in patients with a history of previous hypersensitivity to either of the active ingredients, perindopril or indapamide, or excipient ingredients present in COVERSYL PLUS 5MG/1.25MG or COVERSYL PLUS LD 2.5MG/0.625MG;
- during pregnancy and for lactating women;
- in patients with severe renal insufficiency (creatinine clearance below 30 mL/min); and
- in patients with severe untreated decompensated heart failure.

Related to Perindopril component

Bilateral or unilateral renal artery stenosis.

Previous history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous treatment with an ACE inhibitor (see PRECAUTIONS).

Hypersensitivity to any other ACE inhibitor.

Haemodialysis - Patients haemodialysed using high-flux polyacrylonitrile (“AN69”) membranes 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 (e.g. cuprophane or polysulphone PSF) for haemodialysis.

Related to Indapamide component

History of hypersensitivity to sulphonamides. Anuria, progressive and severe oliguria, hepatic encephalopathy, severe hepatic impairment, hypokalaemia and concomitant administration with non-antiarrhythmic agents causing torsades de pointes.

PRECAUTIONS

There are no special warnings specifically related to the use of COVERSYL PLUS other than those described hereafter for the separate components of the combination.

Specific precautions relating to the use of COVERSYL PLUS are the same as those which apply to the separate components of the combination. Consequently, caution should be observed when the drug is administered in patients with impaired renal function and the risk of hypotension and electrolyte imbalance should be borne in mind (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, and precautions specific to perindopril and indapamide under PRECAUTIONS). The combination of perindopril and indapamide does not exclude the possibility of the onset of lowered potassium levels, in particular in patients with renal impairment. As with any antihypertensive agent containing a diuretic, regular monitoring of plasma levels of potassium should be carried out.
Elderly patients

Renal impairment is commonly observed in elderly people. Care should therefore be taken when prescribing perindopril-containing products to elderly hypertensive patients. The initial dose in the elderly should always be one tablet of COVERSYL PLUS LD 2.5MG/0.625MG daily, and patients should be monitored closely during the initial stages of treatment. (See DOSAGE AND ADMINISTRATION).

COVERSYL PLUS 5MG/1.25MG

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.

COVERSYL PLUS LD 2.5MG/0.625MG

In a randomised double-blind placebo controlled trial (CL3-5590-007) where 193 subjects between 65-85 years old were randomised to receive a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG and 190 subjects were randomised to receive placebo, no subject recorded a serum potassium level of <3.2 mmol/L (the mean baseline-end of study changes, –0.11 mmol/L and –0.07 mmol/L for a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG and placebo respectively).

In the same trial, the safety profile in the sub-group of patients over 75 years old was similar to the adverse event rate of the 65-75 year age group.

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

Fluid and electrolyte imbalance

Patients should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemia, hyperuricaemia, hyperkalaemia (see PRECAUTION below) and hypokalaemia (see PRECAUTION below). Plasma urea and uric acid levels should also be monitored during therapy. Rarely gout has been reported.

The clinical features of electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Potassium levels

The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Lactose intolerance

COVERSYL PLUS 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.

Related to Perindopril component

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 with ACE inhibitors and has been reported on rare occasions with perindopril (see ADVERSE EFFECTS). This may occur at any time during therapy. In such cases treatment 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 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 perindopril 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).

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed following administration of perindopril and may therefore occur. 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.

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 is increased. In all high risk patients it is advisable to initiate treatment with one COVERSYL PLUS LD 2.5MG/0.625MG 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 where hypertensive patients with unilateral or bilateral renal artery stenosis were treated with a dose of perindopril and indapamide equivalent to COVERSYL PLUS 5MG/1.25MG, increases in blood urea, nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of 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 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.

Evaluation of the hypertensive patient should always include an 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 a 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.

Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors. This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

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

There is no experience regarding the administration of perindopril 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 perindoprilat (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 Pharmacokinetics of perindopril). The administration of perindopril leads to the formation of a glucuronon conjugate 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.

Severe cardiac insufficiency (grade IV)

Patients with severe cardiac insufficiency (grade IV) should be monitored closely during the initial stages of treatment. Treatment should be initiated with a reduced dose.

Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Insulin-dependent diabetes mellitus

Patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium) should be monitored closely during the initial stages of treatment. Treatment should be initiated with a reduced dose.

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 depending upon the drug, dosage and duration of use. The incidence of cough reported following administration of a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG was 4.4 %.

The cough is often worse at 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 an 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

Perindopril monotherapy 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 perindopril, 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 PLUS should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procaainamide, 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 PLUS 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 have been reported with another ACE inhibitor and may therefore occur although these have not been reported with a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG.

Rare and sometimes severe skin reactions have been reported following administration of perindopril and may therefore occur (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 high (up to 12.5%) with high doses of one ACE inhibitor and may therefore occur. The actual incidence of taste disturbance is probably low (<0.5%) but data in this respect 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 occurs usually 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 vasodilation. 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.

Related to Indapamide component

Lithium

In general, diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity.

Hypokalaemia

Hypokalaemia is a particular hazard in digitalised patients since dangerous or fatal arrhythmias may be precipitated by it.

Impaired hepatic function

When liver function is impaired, thiazide and thiazide-related diuretics may cause hepatic encephalopathy.
Orthostatic hypotension

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide is given with other non-diuretic antihypertensive agents, the effects on blood pressure are additive.

Lupus erythematosus

Sulphonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. These possibilities should be kept in mind with the use of indapamide although no case has been reported to date.

Photosensitivity

Very rare cases of photosensitivity reactions have been reported. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Impaired renal function

Although indapamide can safely be administered to hypertensive patients with impaired renal function, the treatment should be discontinued if increasing increase in blood nitrogen and oliguria occur. Studies in functionally anephric patients on indapamide monotherapy for one month undergoing chronic haemodialysis have not shown evidence of drug accumulation, despite the fact that indapamide is not dialysable.

Use in Pregnancy – Category D

As this combination contains an ACE inhibitor, COVERSYL PLUS is contraindicated during pregnancy (see CONTRAINDICATIONS).

Related to Perindopril/Indapamide

Reproductive toxicity studies in rats and rabbits showed evidence of increased maternal toxicity and increased embryotoxicity (including delayed foetal development and embryonic deaths) when perindopril and indapamide are given in combination than when each drug is given separately.

Related to Perindopril component

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

As with all ACE inhibitors, COVERSYL PLUS should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with COVERSYL PLUS 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 inhibitor must be discontinued and replaced by another form of treatment. If a patient becomes pregnant while on an ACE inhibitor, she must immediately inform her doctor to discuss a change in medication and further management.

Perindopril or its metabolites have been shown to cross the placenta and distribute to the foetus in pregnant animals. 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
The ACE inhibitor class has also been associated with foetal death *in utero*. ACE inhibitors should not be used in pregnancy.

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.

An 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.

**Related to Indapamide component**

Indapamide or its metabolites have been shown to cross the placenta and distribute in the foetus in pregnant animals. Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should only be given on sound indications, and then in the lowest effective dose.

There is no information on the use of indapamide in pregnancy. Whilst animal studies have not suggested any teratogenic effect, indapamide is not recommended for administration to pregnant women unless the expected benefit outweighs the potential risk.

In animals treated with oral doses of indapamide, a reduction in the number of implantation sites was seen at 25 mg/kg/day and decreases were seen in weight gain of the F1 generation from rats treated at doses \( \geq 2.5 \) mg/kg/day. Galactopoiesis was reduced in the F1 generation from rats treated orally at 0.5 mg/kg/day and this led to increased mortality of the F2 generation during the first 48 hours of life. No embroyotoxicity or teratogenic potential was seen in rats (up to 150 mg/kg/day) or rabbits (up to 180 mg/kg/day).

**Use in Lactation**

COVERSYL PLUS is contraindicated during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue COVERSYL PLUS taking into account the importance of this therapy for the mother.
Related to Perindopril component
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 perindopril 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.

Related to Indapamide component
Indapamide is excreted in human milk during lactation. Other antihypertensive diuretics have been associated during breast-feeding, with decrease or even suppression of milk lactation. Serious adverse reactions might occur in nursing infants such as hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus. COVERSYL PLUS should not be used in lactating women (see Contraindications).

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

Carcinogenicity
Carcinogenicity studies have not been conducted with perindopril arginine. In studies of perindopril erbumine and indapamide hemihydrate, no evidence of carcinogenic activity was observed in mice and rats when indapamide was administered via the diet at levels up to 100 mg/kg/day, or when perindopril erbumine was administered via the drinking water at levels up to 7.5 mg/kg/day for 2 years.

Genotoxicity
Perindopril showed no evidence of genotoxicity potential in assays for gene mutation (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (mouse micronucleus test, Chinese hamster bone marrow cells in vivo, human lymphocytes in vitro) and other genotoxic effects (gene conversion assay in Saccharomyces cerevisiae, unscheduled DNA synthesis in rat hepatic cells). Indapamide was negative in mutagenicity tests in bacteria and in a bone marrow micronucleus test in mice.

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 the ACE inhibitor class 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 as benign. Results from a broad set of assays for gene mutation and chromosomal damage with perindopril arginine suggest no genotoxic potential at clinical doses.

Effects on 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, or at oral indapamide doses up to 25mg/kg/day.

INTERACTIONS WITH OTHER MEDICINES
The combined use of perindopril and indapamide in COVERSYL PLUS is not associated with additional interactions with concomitant drugs other than those known for each of these components.
Shared by Perindopril and Indapamide

Combinations which are NOT RECOMMENDED:

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.

Combinations which require special care:

Baclofen:
Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

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 PLUS 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.

Combinations which require some care:

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).

Corticosteroids, tetracosactide:
Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

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. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Related to Perindopril component

Combinations which are NOT RECOMMENDED:

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 therapy of an ACE inhibitor with a potassium-sparing diuretic (e.g. spironolactone, triamterene, or amiloride), immunosuppressant (e.g. cyclosporin), angiotensin receptor blocker, potassium supplement, 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 should be monitored frequently.

**Antidiabetic agents (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.

**Anaesthetic drugs:**
The ACE inhibitor class may enhance the hypotensive effects of certain anaesthetic drugs.

**Allopurinol, cytostatic or immunosuppressant agents, corticosteroids (main route) or procarbazine:**
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

**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.

**Combinations which require special care:**

**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 excessive hypotensive effects may be minimised by discontinuation of the diuretic and/or ensuring adequate hydration and salt intake prior to commencing therapy with either COVERSYL PLUS 5MG/1.25MG or COVERSYL PLUS LD 2.5MG/0.625MG. 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.

**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.
**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.

**Related to Indapamide component**

No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants, uricosurics and anti-inflammatory agents. It is recommended that the drug not be used in combination with a diuretic agent since the combination may produce hypokalaemia and hyperuricaemia.

**Combinations which require special care:**

**Torsades de pointes inducing drugs:**
Due to the risk of hypokalemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (disopyramide); class III antiarrhythmic agents (amiodarone, sotalol); some neuroleptics (chlorpromazine, thioridazine, trifluoperazine), benzamides (amisulpride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as diphemanil, IV erythromycin, moxifloxacin, pentamidine and methadone. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

**Potassium-lowering drugs:** *amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives:*
Increased risk of low potassium levels (additive effects). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non stimulant laxatives should be used.

**Cardiac glycosides:**
Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

**Combinations which require some care:**

**Potassium-sparing diuretics (amiloride, spironolactone, triamterene):**
The rationale combination, which is useful for some patients, does not exclude the onset of low potassium levels or, particularly in patients with renal insufficiency, raised potassium levels. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

**Metformin:**
Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15mg/L (135µmol/L) in men and 12mg/L (110µmol/L) in women.

**Iodinated contrast media:**
In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.

**Calcium (salts):**
Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

**Cyclosporin:**
Risk of increased creatinine levels with no change in circulating levels of cyclosporine, even when there is no salt and water depletion.
Effects on the ability to drive or operate machinery

Neither of the two active substances nor COVERSYL PLUS affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication. As a result the ability to drive or operate machinery may be impaired.

Effects on laboratory tests

- Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see PRECAUTIONS).
- Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
- Increase in uric acid levels and in blood glucose levels during treatment.
- Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped—this increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
- Increased levels of potassium, usually transitory.
- Rarely, raised plasma calcium levels have been noted.
- Elevation of liver enzymes and serum bilirubin have been reported rarely.

ADVERSE EFFECTS

Adverse experiences have generally been mild and transient and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.1% of patients treated with COVERSYL PLUS 5MG/1.25MG, COVERSYL PLUS LD 2.5MG/0.625MG or placebo.

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide.

Reported with COVERSYL PLUS 5MG/1.25MG
During clinical trials a reduction in potassium levels to less than 3.4mmol/L was observed in 4% of patients taking a dose of perindopril and indapamide equivalent to COVERSYL PLUS 5MG/1.25MG for 12 weeks. After 12 weeks of treatment, the mean reduction in potassium levels was 0.20mmol/L.

Reported with COVERSYL PLUS LD 2.5MG/0.625MG
During clinical trials a reduction in potassium levels (hypokalaemia) to less than 3.4mmol/L was observed in 1.8% of patients taking a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG for 12 weeks. After 12 weeks of treatment, the mean reduction in potassium levels was 0.10mmol/L.

In a specific 15-month placebo-controlled study including 383 elderly patients (over 65 years old), a dose of perindopril and indapamide equivalent to COVERSYL PLUS LD 2.5MG/0.625MG showed a good safety profile in terms of adverse events and laboratory parameters.

In a long-term study involving 165 patients treated with a dose of perindopril and indapamide equivalent to COVERSYL PLUS 5MG/1.25MG for up to one year, the nature and frequency of adverse reactions were similar to those listed above.

The most frequent treatment-emergent adverse reactions (incidence >1%) reported in 3-month controlled clinical trials including a total of 1898 patients treated with a dose of perindopril and indapamide equivalent to either COVERSYL PLUS 5MG/1.25MG or COVERSYL PLUS LD 2.5MG/0.625MG, and 717 patients treated with placebo were as follows:
Treatment-emergent adverse reactions occurring in at least 1% of the patients during the 3-month controlled clinical trials:

<table>
<thead>
<tr>
<th></th>
<th>Perindopril / Indapamide (N=1898)</th>
<th>Placebo (N=717)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cough</td>
<td>83</td>
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<tr>
<td>Headache</td>
<td>59</td>
<td>3.1</td>
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<tr>
<td>Asthenia</td>
<td>30</td>
<td>1.6</td>
</tr>
<tr>
<td>Dizziness, giddiness</td>
<td>26</td>
<td>1.4</td>
</tr>
<tr>
<td>Acute upper resp. influenza infection</td>
<td>22</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The following undesirable effects could be observed during treatment and ranked under the following frequency:

Very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%); very rare (>0.001%, <0.01%), not known (cannot be estimated from the available data).

**Psychiatric and Nervous system disorders:**
*Common*: headache, dizziness, drowsiness, vertigo, paresthesia
*Uncommon*: mood or sleep disturbances (insomnia, dream abnormality), lethargy, anxiety
*Very rare*: depression, confusion, hallucinations

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

**Cardio-vascular disorders:**
*Common*: hypotension whether orthostatic or not (see PRECAUTIONS)
*Uncommon*: palpitations, flushing, impaired peripheral circulation, chest pain, ECG changes (including non-specific ST-T, changes, U waves, left ventricular strain)
*Very rare*: arrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation, angina pectoris, myocardial infarction and 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, bronchitis, upper respiratory acute infection
*Very rare*: eosinophilic pneumonia, rhinitis

**Gastro-intestinal disorders:**
*Common*: constipation, dry mouth, nausea, vomiting, abdominal pain, epigastric pain, anorexia, dysgeusia, dyspepsia, diarrhoea
*Uncommon*: non-infective gastroenteritis and colitis
*Very rare*: pancreatitis

**Hepato-biliary disorders:**
*Very rare*: hepatitis either cytolytic or cholestatic (see PRECAUTIONS), abnormal hepatic function
*Not known*: in case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see PRECAUTIONS)
Skin and subcutaneous tissue disorders:
Common: rash, pruritus, maculopapular eruptions
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see PRECAUTIONS), hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus
Very rare: erythema multiforme, toxic epidermic necrolysis, Steven-Johnson syndrome. Cases of photosensitivity reactions have been reported (see PRECAUTIONS)

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps, weakness of legs
Uncommon: lumbago, joint pain

Renal and urinary disorders:
Uncommon: renal insufficiency, cystitis, polyuria.
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence, modification of libido

General disorders:
Common: asthenia
Uncommon: sweating, atypical chest pain

Blood and the lymphatic system disorders:
Very rare: decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia. Anaemia (see PRECAUTIONS) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis) and in patients with congenital G-6PDH deficiency (see PRECAUTIONS).

Metabolism and nutrition disorders:
Rare: hypercalcemia

Post marketing experience (frequency unknown)
Investigations: Electrocardiogram QT prolonged. Blood glucose increased and blood uric acid increased during treatment. Elevated liver enzyme levels. Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped, this increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.

Metabolism and nutrition disorders: Potassium depletion with hypokalaemia particularly serious in certain high risk populations (see PRECAUTIONS). Increased levels of potassium, usually transitory. Hyponatraemia with hypovolaemia responsible for dehydration and orthostatic hypotension.

Nervous system disorders: Syncope
Cardiac disorders: Torsades de points (potentially fatal).

DOSAGE AND ADMINISTRATION

COVERSYL PLUS 2.5MG/0.625MG
Treatment should be started at the normal dose of one COVERSYL PLUS LD 2.5MG/0.625MG tablet per day as a single dose, to be taken in the morning before a meal.

In cases where target blood pressure is not achieved, the dose should be titrated to one tablet of COVERSYL PLUS 5MG/1.25MG daily.
**Elderly Patients**

Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing perindopril-containing products to elderly hypertensive patients.

The initial dose in the elderly should always be one tablet of COVERSYL PLUS LD 2.5MG/0.625MG daily, and patients should be monitored closely during the initial stages of treatment.

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

**Patients with Renal Insufficiency**

In cases of severe renal insufficiency (creatinine clearance below 30mL/min), the treatment is contraindicated.

In patients with moderate renal insufficiency (creatinine clearance 30-60mL/min), the maximum dose should be one tablet of COVERSYL PLUS LD 2.5MG/0.625MG per day.

In patients with a creatinine clearance greater than or equal to 60mL/min, no dose adaptation is required.

Normal medical practice includes periodic control for creatinine and potassium.

**Patients with hepatic impairment**

In severe hepatic impairment, treatment is contraindicated.
In patients with moderate hepatic impairment, no dose modification is required.

**OVERDOSAGE**

The most likely adverse event in cases of overdose is hypotension, with the possibility of nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, polyuria or oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

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. 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.

Perindoprilat, the active form of perindopril, can be dialysed (see Pharmacokinetics of perindopril).
PRESENTATION AND STORAGE CONDITIONS

Presentation

COVERSYL PLUS 5MG/1.25MG
White rod-shaped tablets, containing 5mg of perindopril arginine and 1.25mg of indapamide hemihydrate.

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

COVERSYL PLUS LD 2.5MG/0.625MG
White, rod-shaped, scored tablets, containing 2.5mg of perindopril arginine and 0.625mg of indapamide hemihydrate.

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

Storage Conditions

Store in a dry place below 30ºC. Keep the container tightly closed. Shelf-life when stored as recommended: 3 years

NAME AND ADDRESS OF THE SPONSOR

Servier Laboratories (Australia) Pty Ltd
8 Cato Street
PO Box 196
HAWTHORN VIC 3122
ABN 54 004 838 500

POISONS SCHEDULE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
31 January, 2007

DATE OF MOST RECENT AMENDMENT
24 August, 2012

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