

COVERSYL[®] PLUS

Data Sheet

NAME OF THE DRUG

COVERSYL PLUS

Perindopril erbumine 4mg / Indapamide hemihydrate 1.25mg

DESCRIPTION

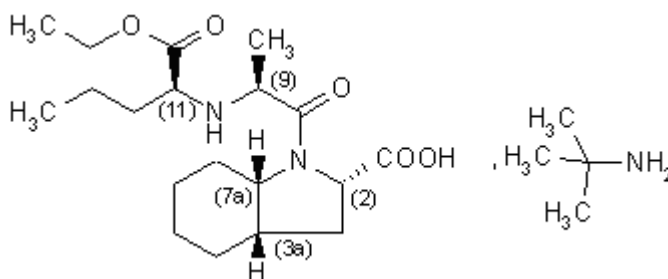
Active Ingredients

Perindopril erbumine is a dipeptide monoacid monoester with a perhydroindole group and no sulphhydryl radical; chemical name, tert-butylammonium (2S, 3aS, 7aS)-1-(N-[(S)-1-ethoxycarbonyl butyl]-L-alanyl) perhydroindole-2-carboxylate. Perindopril erbumine is a white powder, readily soluble in purified water, ethanol and chloroform. Perindopril has five asymmetric centres and is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

CAS Registry Number : 107133-36-8

Molecular formula : C₁₉H₃₂N₂O₅, C₄H₁₁N

Chemical structure :



Indapamide is a non thiazide indole derivative of chlorosulphonamide; chemical name 4-chloro-N-(2-methyl-1-indoliny)-3-sulphamoyl benzamide 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 : C₁₆H₁₆ClN₃O₃S, ½ H₂O

Chemical structure :



Excipients

Cellulose - microcrystalline, lactose, magnesium stearate, silica - colloidal anhydrous.

PHARMACOLOGY

Pharmacological Mechanism of Action

COVERSYL PLUS is a combination of perindopril erbumine, an angiotensin converting enzyme (ACE) inhibitor, and indapamide, a chlorosulphamoyl diuretic, in which the doses of the ACE inhibitor and diuretic components are up to two times lower than the usual dose 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 kaliuresis or uric acid excretion. Only at doses greater than 2.5mg/day, ie. at doses of indapamide two times greater than the amount present in one COVERSYL PLUS 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, COVERSYL PLUS has greater toxicity than that of each individual component. Renal manifestations of the effects of perindopril in the rat are increased when the drug is given in combination with indapamide (about 3 fold relative to the effects 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 their pharmacokinetic properties by comparison to separate administration.

In a bioequivalence study comparing perindopril 4mg and indapamide 1.25mg (as single component capsules) with the fixed dose formulation (COVERSYL PLUS) the pharmacokinetics of each active ingredient were shown to be predominantly unchanged. Bioequivalence was established based on AUC and C_{max} . Only the T_{max} of indapamide was shorter after administration of the COVERSYL PLUS tablet.

Dose form, active ingredient	Plasma C_{max} (ng/mL)	Plasma AUC (ng/mL.h)	Plasma T_{max} (h)
Perindopril capsule	64 ± 24 (range 35-129)	102 ± 43 (range 56-226)	0.75 (range 0.33–1.5)
Indapamide capsule	15 ± 3.7 (range 9.7-24)	298 ± 79 (range 194-466)	2.0 (range 1.5-6.0)
Combination tablet - perindopril	72 ± 20 (range 44-117)	106 ± 32 (range 68-181)	0.75 (range 0.33–1.5)
- indapamide	17 ± 3.6 (range 13-26)	294 ± 79 (range 182-481)	1.5 (range 1.0–3.0)

Pharmacokinetics of Perindopril

Following oral administration, perindopril is rapidly absorbed and is 61-85% bioavailable. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1

hour. Biotransformation of perindopril to the active metabolite perindoprilat is approximately 20%. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of perindopril and peak pharmacological activity occurs after 4 to 6 hours. Protein binding of perindoprilat is below 30%. Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The elimination half-life of the free fraction is between 3 and 5 hours. The terminal half-life which corresponds to the dissociation of perindoprilat from ACE, is approximately 25 to 30 hours. When perindopril is administered chronically, steady-state perindoprilat concentration 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 glucuronoconjugate 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.

Plasma elimination half life of unchanged indapamide is biphasic with 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*). 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

Essential hypertension.

COVERSYL PLUS is indicated for use in second-line therapy for the treatment of essential hypertension, where blood pressure has not been adequately controlled by monotherapy.

CONTRAINDICATIONS

Relating to COVERSYL PLUS

COVERSYL PLUS is contraindicated:

patients with a history of previous hypersensitivity to either of the active ingredients, perindopril or indapamide, or excipient ingredients present in COVERSYL PLUS;
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 *WARNINGS AND 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.

WARNINGS AND PRECAUTIONS

Related to COVERSYL PLUS

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 *WARNINGS AND 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 the perindopril 2mg / indapamide 0.625mg fixed dose combination product 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.

Fluid and electrolyte imbalance

Patients should be monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatraemia, hypochloreaemia, hyperuricaemia, hyperkalaemia (see *PRECAUTIONS* below) and hypokalaemia (see *WARNINGS AND PRECAUTIONS* below). Plasma urea and uric acid levels should also be monitored during therapy.

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.

Rarely gout has been reported.

Related to Perindopril component

Hyperkalaemia

Diabetics and particularly the elderly may be at increased risk of hyperkalaemia. However, hyperkalaemia (>5.5mmol/L) is more likely in patients with some degree of renal impairment or those treated with potassium-sparing diuretics or with potassium supplements and/or consuming potassium containing salt substitutes. In some patients, hyponatraemia may co-exist with hyperkalaemia.

Angio-oedema

Severe 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 nonpitting oedema of the skin mucous membrane and subcutaneous tissue.

Angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients with ACE inhibitors and has been reported on rare occasions with perindopril. 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. Angioedema 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.

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.

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 *WARNINGS AND 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 tablet of the perindopril 2mg / indapamide 0.625mg fixed dose combination product.

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 COVERSYL PLUS, 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.

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*). 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 70mL/min.

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.

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_{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 glucuronoconjugate 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.

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 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 (<1gram per 24 hours). However in the majority of patients with pre-existing proteinuria treated with perindopril, proteinuria disappeared or remained stable.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression (including leucopenia/neutropenia) have been reported with the ACE inhibitor class. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leukopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine $\geq 180\mu\text{mol/L}$) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Dermatological reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have 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 high (up to 12.5%) with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data in this respect is 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. If perioperative hypotension occurs, volume expansion would be required.

Valvular stenosis

There has been some concern on theoretical grounds that patients with aortic stenosis 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.

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.

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 should not be used during pregnancy.

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

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 foetus.

The ACE inhibitor class has also been associated with foetal death *in utero*. ACE inhibitors should not be used in pregnancy.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal hypotension, renal failure, skull hypoplasia 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. 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 25mg/kg/day and decreases were seen in weight gain of the F1 generation from rats treated at doses ≥ 2.5 mg/kg/day. Galactopoiesis was reduced in the F1 generation from rats treated orally at 0.5mg/kg/day and this led to increased mortality of the F2 generation during the first 48 hours of life. No embryotoxicity or teratogenic potential was seen in rats (up to 150mg/kg/day) or rabbits (up to 180 mg/kg/day).

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 not known whether indapamide is excreted in breast milk. It is therefore recommended that COVERSYL PLUS should not be given to lactating women as the possible effect on the newborn is unknown.

Paediatric Use

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

Carcinogenicity, Genotoxicity, Impairment of Fertility

No carcinogenicity or genotoxicity studies of perindopril in combination with indapamide have been conducted, and the effect of the combination on fertility has not been investigated.

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.

In studies of the component drugs, 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 was administered via the drinking water at levels up to 7.5 mg/kg/day.

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.

Studies in rats showed no impairment of male or female fertility at oral perindopril 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:

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, as is the case in this combination, the risk of lithium toxicity may be increased.

Combinations which require special care:

Baclofen:

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

N.S.A.I.D (systemic route), high-dose salicylates:

Acute renal insufficiency in dehydrated patients (reduction in glomerular filtration). The patient should be well hydrated; renal function should be monitored at the start of treatment.

Combinations which require some care:

Neuroleptics, imipramine-like antidepressants (tricyclics):

Increased antihypertensive effect and risk of orthostatic hypotension due to additive effect.

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.

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. The concomitant therapy of an ACE inhibitor with a potassium-sparing diuretic (e.g. spironolactone, triamterene, or amiloride), potassium

supplement, or potassium-containing salt substitute can increase the risk of hyperkalaemia, therefore 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).

Anaesthetic drugs:

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

Allopurinol, cytostatic or immunosuppressant agents, corticosteroids (main route) or procainamide:

Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Antihypertensive agents

The concomitant administration of antihypertensive agents may increase the hypotensive effect of ACE inhibitors.

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 ensuring adequate hydration and salt intake prior to commencing COVERSYL PLUS therapy. The patient should be closely observed for several hours following the initial dose 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.

Related to Indapamide component

No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants and uricosurics. 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 are NOT RECOMMENDED:

Non antiarrhythmic drugs which lengthen the QT interval or cause torsades de pointes (astemizole, erythromycin IV, pentamidine, terfenadine):

Torsades de pointes (low potassium levels is a risk, as are bradycardia and pre-existing long QT interval). Substances which do not have the unwanted effect of causing torsades de pointes should be used in cases of low potassium levels.

Combinations which require special care:***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.

N.S.A.I.D (systemic route), high-dose salicylates:

Possible reduction in the antihypertensive effect of indapamide. Acute renal insufficiency in dehydrated patients (reduction in glomerular filtration). Hydrate the patient ; monitor renal function at the start of treatment.

Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives:

Increased risk of low potassium levels (additive effect). 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.

Antiarrhythmic drugs which produce torsades de pointes: Class IA antiarrhythmic agents (quinidine, disopyramide), amiodarone, sotalol:

Torsades de pointes (low potassium levels is a risk factor, as are bradycardia and a pre-existing long QT interval). Prevention of low potassium levels and correction if necessary: monitoring of the QT interval. Antiarrhythmics should not be administered in cases of torsades de pointes (management by pacemaker).

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 cyclosporin, 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

The most common adverse effect is hypokalaemia

Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.

Increase in uric acid levels and blood glucose levels.

Altered high potassium levels, usually transitory, have been noted.

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, renovascular hypertension and severe heart failure.

Rarely, raised plasma calcium levels have been noted.

Elevation of liver enzymes and serum bilirubin have been reported rarely.

ADVERSE REACTIONS**Reported with COVERSYL PLUS**

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. During clinical trials a reduction in potassium levels to less than 3.4mmol/L was observed in 4% of patients taking COVERSYL PLUS for 12 weeks. After 12 weeks of treatment, the mean reduction in potassium levels was 0.20mmol/L.

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 both the combination or placebo.

The most frequent treatment-emergent adverse reactions (incidence >1%) reported in 3-month controlled clinical trials including a total of 1898 patients treated with the combination (both perindopril 2mg / indapamide 0.625mg and perindopril 4mg / indapamide 1.25mg) 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:

	Perindopril / Indapamide (N=1898)		Placebo (N=717)	
	n	%	n	%
Cough	83	4.4	15	2.1
Headache	59	3.1	41	5.7
Asthenia	30	1.6	14	2.0
Dizziness, giddiness	26	1.4	4	0.6
Acute upper resp. influenza infection	22	1.2	10	1.4

Hyponatraemia and Hypokalaemia have been reported rarely during clinical use of COVERSYL PLUS.

Constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains and taste disturbances have been reported commonly following treatment with COVERSYL PLUS.

Other treatment-emergent adverse reactions reported uncommonly, and which occurred more often on drug than placebo, are listed hereafter by body system:

GI system:, vomiting, dyspepsia, disorders of stomachal function, non infective gastroenteritis and colitis, diarrhoea, pancreatitis

Musculo-skeletal: lumbago, pain of joint

Respiratory system: bronchitis, rhinitis, upper respiratory acute infection

Skin and subcutaneous tissue: hypersensitivity reactions, maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus, angioneurotic oedema

Musculoskeletal, connective tissue and bone: muscle cramps, paresthesia

Blood and lymphatic system: thrombocytopenia, leucopenia/neutropenia, agranulocytosis, anaemia (whether haemolytic, aplastic or not)

Vascular disorders: palpitations, flushing, impaired peripheral circulation

Respiratory system: discomfort on exertion, epistaxis

General symptoms: atypical chest pain, orthostatic faintness

Reported with Perindopril component

Adverse events other than those listed above for the combination product 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 and Nervous system disorders:

Common: vertigo, paresthaesia

Uncommon: mood or sleep disturbances

Very rare: confusion

Ear /labyrinth and Eye disorders:

Common: tinnitus, vision disturbance

Vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients

Respiratory, thoracic and mediastinal disorders:

Common: dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia

Gastro-intestinal disorders:

Common: dysgeusia

Hepato-biliary disorders:

Very rare: hepatitis, either cytolytic or cholestatic

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria,

Very rare: erythema multiforme

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:
Uncommon: sweating
Blood and the lymphatic system disorders:
Very rare: decreases in haemoglobin and haematocrit

Reported with Indapamide component

Adverse reactions other than those listed above for the combination product and that have been reported in studies with indapamide 2.5mg immediate-release or 1.5mg sustained-release tablets include the following:

Incidence <1 %:

Cardiovascular: chest pain, palpitations, ECG changes (including non-specific ST-T changes, U waves, left ventricular strain), orthostatic hypotension, tachycardia

GI system: dry mouth, gastralgia, constipation, abdominal pain

Metabolic disorders: gout

Nervous system: visual disturbances, drowsiness, sleepiness, insomnia, weakness, lethargy, fatigue, anxiety

Skin and appendages: sweating, pruritus, rash

Special senses: tinnitus

Urogenital: modification of libido, cystitis, polyuria, impotence

Incidence <5 %:

Musculoskeletal: muscle cramps, back pain, weakness of legs

DOSAGE AND ADMINISTRATION

One COVERSYL PLUS tablet per day as a single dose, preferably to be taken in the morning.

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 the perindopril 2mg / indapamide 0.625mg fixed dose combination product 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 the perindopril 2mg / indapamide 0.625mg fixed dose combination product per day.

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

Normal medical practice includes periodic control for creatinine and potassium.

Other 'at risk' populations

In patients with severe cardiac insufficiency (grade IV) or insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started with a reduced initial dose, and patients should be monitored closely during the initial stages of treatment.

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.

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension is produced, this can be treated by placing the patient in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialysed (see *Pharmacokinetics of perindopril*).

PHARMACEUTICAL PRECAUTIONS

Keep out of reach of children. Store below 30°C. This medicine should not be used after the expiry date shown on the pack.

PRESENTATION

White rod-shaped tablets, containing 4mg of perindopril erbumine and 1.25mg of indapamide hemihydrate.

PACKAGE QUANTITIES

Supplied in a blister pack of 30 tablets.

MEDICINE CLASSIFICATION

Prescription Medicine

FURTHER INFORMATION

Nil

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