COVAPRIL TABLET 4MG

DESCRIPTION: An oblong, scored, white to off-white tablet.

COMPOSITION: Each tablet contains: Perindopril Erbumine 4mg.

PHARMACODYNAMICS: Perindopril following hydrolysis to perindoprilat, inhibits angiotensin converting enzyme (ACE) both in vitro and in vivo. It is thought that ACE inhibitors reduce blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increased plasma renin activity and a decrease in aldosterone. In addition to its effects on circulating ACE, 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. 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. 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.

PHARMACOKINETICS: Following oral administration, Perindopril is rapidly absorbed and is 61-85% bioavailable. Elimination is rapid, occurring predominantly via the urine. Plasma t 1/2 = 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 of perindoprilat is reached within 4 days, and perindoprilat does not accumulate. Food intake may reduce hepatic biotransformation to perindoprilat. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure (see Dosage and Administration). Apart from perindoprilat, the administration of perindopril leads to the formation of 5 other metabolites, all of which are inactive and exist in very low quantities. One of these is the 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.

INDICATIONS:
1. Hypertension: Treatment of hypertension
2. Heart failure: Treatment of symptomatic heart failure
3. Stable coronary artery disease: Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularization

RECOMMENDED DOSAGE: It is recommended that Perindopril Erbumine is taken once daily in the morning before a meal. The dose should be individualised according to the patient profile and blood pressure response.
Hypertension: Perindopril Erbumine may be used in monotherapy or in combination with other classes of antihypertensive therapy. The recommended starting dose is 4 mg given once daily in the morning. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with Perindopril Erbumine; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril Erbumine.
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril Erbumine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril Erbumine should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure: It is recommended that Perindopril Erbumine, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision.
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril Erbumine. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril Erbumine.
Stable coronary artery disease: Perindopril Erbumine should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.
Dosage adjustment in renal impairment: Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

Creatinine Clearance (ml/min)	Recommended dose
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

Dosage adjustment in hepatic impairment: No dosage adjustment is necessary in patients with hepatic impairment.
Paediatric use: Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:
- History of previous hypersensitivity to Perindopril or to any component of the formulation, nursing mothers, bilateral or unilateral renal artery stenosis.
- Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor (see Warnings).
- 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 (eg. cuprophane or polysulphone PSF) for haemodialysis.
- Pregnancy
- The concomitant use of Covapril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m2) (see Interactions).

WARNING & PRECAUTIONS **Angioedema:** Severe life-threatening angioedema has been reported with most of the ACE The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema is nonpitting oedema of the skin mucous membrane and subcutaneous tissue. Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors and has been reported on rare occasions with Perindopril. In such cases Perindopril 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 angioedema 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 angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. Angioedema may occur with or without urticaria. There are reports when changing a patient to another ACE inhibitor was followed by recurrence of angioedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema, to a drug of this class (see Contraindications).
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 or those treated vigorously with diuretics or after severe diarrhoea or patients on dialysis. (See Precautions, Drug Interactions and Adverse Reactions). Administration of 2 mg Perindopril to patients with mild-moderate heart failure was not associated with any significant reduction in blood pressure. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.
Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of Perindopril and/or diuretic is increased. In all high risk patients it is advisable to initiate treatment with Perindopril at the lowest dose. 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, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. The increases in hypertensive patients with unilateral or bilateral renal artery stenosis, in blood urea, nitrogen and serum creatinine are usually reversible upon discontinuation of ACE treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors. Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.
Evaluation of the hypertensive patient should always include assessment of renal function (see Dosage and Administration). 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.
Some ACE inhibitors have been associated with the occurrence of proteinuria and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac-reserve, or treatment with a non-steroidal anti-inflammatory drug. Perindopril is dialysable with a clearance of 70 ml/min.
Impaired Hepatic Function: Biotransformation of perindopril to perindoprilat mainly occurs in the liver. Kinetic parameters of perindopril were not modified by hepatic failure. With the exception of bioavailability which was increased, kinetic parameters of perindoprilat (including tmax) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (see Pharmacokinetics). 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.

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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 side-effect of ACE inhibitor therapy.The cough is often worse when lying down or at night, and has been reported more frequently in women. Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.
The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.
Proteinuria: Perindopril treatment has occasionally been associated with mild or transient proteinuria (< 1 gram/per 24 hours). However in the majority of patients with pre-existing proteinuria treated with 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: Agranulocytosis and bone marrow depression (including leucopenia/neutropenia) have been reported with ACE inhibitors. 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 ³180 umol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.
Hyperkalaemia: Since ACE inhibitors reduce Angiotensin II formation resulting in decreased production of aldosterone, an increase in serum potassium may be observed. However, hyperkalaemia (>5.5mEq/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. Diabetics and elderly patients, particularly those who are elderly may be at increased risk. 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.
Dermatological Reactions: Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc). A causal relationship is difficult to assess.
Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.
Taste Disturbances (Dysgeusia): Taste disturbances were reported to be high with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low but data in this respect is scarce and difficult to interpret. Taste disturbances with ACE inhibitors are described as suppression of taste or a metallic sensation in mouth. The dysgeusia occurs usually in the first weeks of treatment and may disappear in most cases within 1-3 months of treatment.
Lipid Profile: No significant change in total cholesterol and triglycerides with Perindopril therapy.
Elderly Patients: Renal insufficiency is commonly observed in elderly people. Care should therefore be taken when prescribing Perindopril to elderly hypertensive patients. The initial dose of Perindopril in the elderly should always be 2 mg daily and patients should be monitored closely during the initial stages of treatment. (See `Dosage and Administration').
Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.
Agents Causing Renin Release: The effect of perindopril may be enhanced by concomitant administration of antihypertensive agents which cause renin release.
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 vasodilatation. The true clinical importance of this concern is uncertain.
Paediatric Use: Use not recommended as no data is available in children.
Use in Pregnancy: Increased risk of birth deffects, fetal and neonatal morbidity and death when used throughout pregnancy.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS):There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Interactions).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
Warning:- ACE inhibitors have been shown to be strongly fetotoxic in animal studies. Recently available data indicate that ACE inhibitors can cause foeta and neonatal morbidity and mortality when administered to pregnancy woman. The use of these agents during pregnancy is not recommended.
-Increased risk of birth defects, fetal and neonatal morbidity and death when used throughout pregnancy.

INTERACTION WITH OTHER MEDICATIONS: Diuretics: When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, 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.
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, the risk of lithium toxicity may be increased.
Agents affecting serum potassium: ACE inhibitors 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.
Non-steroidal anti-inflammatory drugs: Drugs with prostaglandin synthetase inhibitor properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between Perindopril or indomethacin or other non-steroidal anti-inflammatory drugs.
Tetracycline and other drugs that interact with magnesium: The simultaneous administration of tetracycline with an ACE inhibitor may significantly reduce the absorption of tetracycline, possibly due to the magnesium content in the ACE inhibitor tablets. This interaction should be considered if co-prescribing an ACE inhibitor and tetracycline or other drugs that interact with magnesium.
Agents Affecting Sympathetic Activity: As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with concomitant administration of a drug with sympathetic activity and Perindopril.
Antihypertensive agents and vasodilators: Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.
Antidiabetic agents: Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.
Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates: Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.
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.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Contraindications and Warnings/Precautions).

USE IN PREGNANCY & LACTATION:
Use in Pregnancy: All ACE Inhibitor should not be used in pregnancy. Increased risk of birth deffects, fetal and neonatal morbidity and death when used throughout pregnancy.
Use in Lactation: Contraindicated.

SIDE EFFECTS: The following undesirable effects have been observed during treatment with perindopril and 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), including isolated reports.
Psychiatric disorders: *Uncommon:* mood or sleep disturbances
Nervous system disorders: *Common:* headache, dizziness, vertigo, paresthaesia.*Very rare:* confusion
Eye disorders: *Common:* vision disturbance
Ear and labyrinth disorders: *Common:* tinnitus
Cardio-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:* cough, dyspnoea.*Uncommon:* bronchospasm.*Very rare:* eosinophilic pneumonia, rhinitis.
Gastro-intestinal disorders: *Common:* nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation.*Uncommon:* dry mouth.*Very rare:* pancreatitis.
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: *Common:* asthenia.*Uncommon:* sweating
Blood and the lymphatic system disorders: Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported.
Investigations: Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

SYMPTOMS AND TREATMENT OF OVERDOSE: Isolated cases of overdosage have been reported to date. The signs, which are most likely to appear in the case of overdosage are those of hypotension. In the case of overdosage, gastric washout and intravenous infusion of a normal saline solution are recommended. The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

STORAGE CONDITIONS: Store below 30°C. Protect from light and moisture. Keep out of reach of children. *Jauhkan daripada kanak-kanak*.

PACK SIZE: 3 x 10's & 10 x 10's per box.

SHELF LIFE: Please refer outer package. To be consumed within 6 months after opening the aluminium pouch.

Product Registration Holder:
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Size: 170mm(W) x 250mm(H)