SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

PERISTAR 2 Tablets

PERISTAR 4 Tablets

PERISTAR 8 Tablets

COMPOSITION

Each **PERISTAR 2** tablet contains 2 mg perindopril tert-butylamine salt.

Each **PERISTAR 4** tablet contains 4 mg perindopril tert-butylamine salt.

Each **PERISTAR 8** tablet contains 8 mg perindopril tert-butylamine salt.

List of excipients: Hydrophobic colloidal silica, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION

Perindopril inhibits angiotensin I converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Pharmacokinetics:

Given orally the peak concentration of perindoprilat, the active metabolite, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours. Although the oral bioavailability of

perindopril (75 %) is not affected by food, the bioavailability of perindoprilat is reduced by approximately 35 %.

Perindopril is metabolized to perindoprilat and to five other inactive metabolites.

Perindoprilat is about 10 % to 20 % bound to plasma proteins. Perindoprilat binds to angiotensin converting enzyme at both plasma and tissue levels.

About 75 % of an oral dose of perindopril is excreted in the urine as unchanged drug, as perindoprilat, and as other metabolites; the remainder is excreted in the faeces. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 - 30 hours. Elimination of perindoprilat is less in the patients with cardiac or renal failure and in the elderly patients. In these cases dosage adjustment should be applied in relation to the degree of reduction in creatinine clearance.

INDICATIONS

PERISTAR is indicated for:

- Mild to moderate hypertension and
- Heart failure not adequately controlled by conventional therapy with diuretics and digitalis and in whom vasodilatation is indicated.

CONTRA-INDICATIONS

- Sensitivity to any of the components of **PERISTAR**.
- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotensin receptor blocker.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.

WARNINGS

Should a woman become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and changed to a different medicine (see PREGNANCY AND LACTATION).

If a woman is contemplating pregnancy, a different class of medicine should be used (see PREGNANCY AND LACTATION).

PERISTAR should be used with caution in the following conditions:

- Cerebrovascular disease or ischemic heart disease – Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular incidents.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting) – Although it may occur in normovolumic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of **PERISTAR** induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatraemia should have these conditions corrected before therapy with **PERISTAR.** Monitoring is required after initiating therapy.
- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with **PERISTAR** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/l or doubling of the pre-treatment value) then **PERISTAR** may need to be withdrawn (see CONTRA-INDICATIONS).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- Hypotension in acute myocardial infarction - Treatment with **PERISTAR** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mmHg

or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 2 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg or more than 1 hour) then **PERISTAR** should be withdrawn.

- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia – **PERISTAR** may cause an increase in serum potassium levels.
- Renovascular disease – **PERISTAR** should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance **PERISTAR** should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see DOSAGE AND DIRECTIONS).
- Renal artery stenosis, bilateral or in one kidney or renal transplant – Increased risk of renal function impairment may cause increases in blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.
- Renal function impairment – Decreased elimination of **PERISTAR** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.
- Anaphylactoid reactions have occurred in patients using ACE inhibitors, including **PERISTAR**, during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulphate absorption.
- Hypersensitivity / angioedema - If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with **PERISTAR**, **PERISTAR** should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.
- Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, it is likely to cause airway obstruction, and appropriate emergency therapy should be administered. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and

sustained resolution of symptoms has occurred. **These patients should never receive any PERISTAR, ACE-Inhibitors or angiotensin-receptor blockers again.**

- **PERISTAR** causes a higher rate of angioedema in black patients than in non-black patients.
- Safety and efficacy in children has not been established.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrythmias and cardiac arrest.

INTERACTIONS

Concomitant use of **PERISTAR** with:

- Diuretics, alcohol and hypotension-producing medications – The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- Loop, thiazide or related diuretics – "First dose hypotension" may occur (see DOSAGE AND DIRECTIONS FOR USE).
- Indomethacin and non-steroidal anti-inflammatory medicines (NSAIDs) - reduce the antihypertensive effects of **PERISTAR.** Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **PERISTAR.**
- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride – Concurrent administration may result in hyperkalaemia.
- Lithium – Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.

PREGNANCY AND LACTATION

Use of **PERISTAR** limited to the first trimester does not appear to present a significant risk to the foetus, but foetal exposure after this time has been associated with teratogenicity and severe toxicity in the foetus and newborn, including death. **PERISTAR** crosses the placenta. Foetal exposure to ACE inhibitors during the second and third trimester can cause hypotension, renal failure, anuria, skull hypoplasia, hyperkalaemia and oliguria. Oligohydramnios may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation.

Infants who have been exposed *in utero* to **PERISTAR** should be closely monitored.

Peritoneal dialysis may be of some benefit in the clearance of **PERISTAR** from the neonatal circulation.

Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

PERISTAR should be taken before meals at the same time every day.

Mild to moderate hypertension

The recommended dosage is 4 mg orally taken in the morning before breakfast which can be increased to a single dose of 8 mg if necessary after one month of treatment.

In the elderly patients and in cardiac failure substantially lower dosage should be used because of impaired clearance.

Insulin and non-insulin dependent diabetics can be treated with the usual doses.

Congestive heart failure

The treatment should be initiated under close medical supervision. Initial dose of 2 mg orally as a single dose in the morning which may, in most instances, be increased to 4 mg (once blood pressure acceptability has been demonstrated).

Concomitant diuretic therapy in hypertension

Caution is recommended in patients who are currently being treated with diuretics. As the effects of ACE inhibitors may be potentiated in a situation where hypovolaemia may occur, the diuretic therapy should be discontinued prior to initiation of therapy with **PERISTAR.** In the case of combination with a diuretic it is not advisable to prescribe a potassium salt or a potassium sparing agent before assay of blood potassium and attention should be paid to possible overdosage of the diuretic.

Renal insufficiency

In patients with renal insufficiency, the dosage of **PERISTAR** must be adjusted in relation to the severity of the insufficiency. The following dosages may be recommended:

Creatinine clearance	Recommended dosage
Between 30 and 60 ml/min	2 mg per day
Between 15 and 30 ml/min	2 mg per day every other day
< 15 ml/min	2 mg on day of dialysis

Perindopril is dialysable (70 ml/min).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Cardiac disorders

Less frequent: Hypotension (dizziness, light-headedness or fainting); chest pain; congestive heart failure.

The following have been reported but the frequency is unknown:

Palpitations.

Immune system disorders

Less frequent: Hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema. A symptom complex has been reported which may include: fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Blood disorders

Less frequent: Hyperkalaemia; neutropenia or agranulocytosis (fever and chills).

Nervous system disorders

Frequent: Headache; dizziness.

Less frequent: Fatigue; paraesthesia.

The following have been reported but the frequencies are unknown:

Mood and/or sleep disturbances.

Endocrine disorders

Less frequent: Pancreatitis.

Respiratory disorders

Frequent: Dry, persistent cough.

Gastrointestinal disorders

Less frequent: Diarrhoea; nausea; stomach pain.

The following have been reported but the frequency is unknown:

Unspecific digestive disorders.

Reproductive system disorders

The following have been reported but the frequency is unknown:

Sexual disorders.

Musculoskeletal disorders

The following has been reported but the frequency is unknown:

Asthenia.

Renal disorders

Less frequent: Uraemia; increased creatinine concentrations; renal dysfunction; reversible acute renal failure.

Skin disorders

Less frequent: Rash; erythema multiforme; toxic epidermal necrolysis; photosensitivity; alopecia.

General disorders

Less frequent: Dysgeusia (loss of taste).

Special precautions:

Myocardial infarction and cerebrovascular incidents may be due to severe falls in blood pressure in high-risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.

In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **PERISTAR** or diuretic is adjusted.

If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9% saline.

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when **PERISTAR** has been given concomitantly with a diuretic. Dosage reduction or discontinuation of **PERISTAR** or the diuretic may be required.

Signs of facial or extremity swelling or difficulty in swallowing or breathing, required immediate medical attention, because of the risk of angioedema.

Caution when driving or performing tasks requiring alertness because of possible dizziness.

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **PERISTAR** may block angiotensin II formation secondary to complementary renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See SIDE EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdose:

Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdose:

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct

hypotension and treating dehydration and electrolyte imbalances. **PERISTAR** is removable by haemodialysis.

IDENTIFICATION

PERISTAR 2: White to off-white, round, biconvex tablet, plain on one side and debossed with '2' on other side.

PERISTAR 4: White to off-white, capsule shaped tablets, with a break line on both sides and debossed with '4' on either side of the breakline on one side of the tablets.

PERISTAR 8: White to off-white, biconvex tablet, plain on one side and debossed with '8' on other side.

PRESENTATION

PERISTAR 2: Transparent clear PVC / Aclar / plain aluminium foil blister strips, each containing 30 tablets. One blister strip is packed in an aluminium laminated pouch with a desiccant enclosed. The pouch is placed in an outer carton bearing the labelling requirements.

PERISTAR 4: Transparent clear PVC / Aclar / plain aluminium foil blister strips, each containing 30 tablets. One blister strip is packed in an aluminium laminated pouch with a desiccant enclosed. The pouch is placed in an outer carton bearing the labelling requirements.

PERISTAR 8: Transparent clear PVC / Aclar / plain aluminium foil blister strips, each containing 15 tablets. One blister strip is packed in an aluminium laminated pouch with a desiccant enclosed. Two pouches are placed in an outer carton bearing the labelling requirements.

STORAGE

Store at or below 25 ºC in a dry place. Protect from light.

Keep the blister in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

PERISTAR 2: 41/7.1.3/0694

PERISTAR 4: 41/7.1.3/0695

PERISTAR 8: 41/7.1.3/0696

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