

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Daren[®]. (Daren[®] is marketed as Renil[®] in Malta)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

There are four strengths of Daren[®] Tablets available. Each contains 2.5 mg, 5 mg, 10 mg and 20 mg enalapril maleate.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Daren 2.5 mg: White, round, flat tablets, 6 mm in diameter.

Daren 5 mg: White, round, flat, scored tablets, 8 mm in diameter.

Daren 10 mg: Pink, round, flat, scored tablets, 7 mm in diameter.

Daren 20 mg: Light orange, round, flat, scored tablets, 9 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Daren is indicated for the treatment of hypertension and heart failure.

4.2 Posology and method of administration

Dosage for adults:

Hypertension: The usual initial dose is 10-20 mg once daily. A daily dose exceeding 40 mg is not recommended.

Heart failure: The initial dose is 2.5 mg daily, which can be increased gradually over a period of 2-4 weeks. The usual maintenance dose is 20 mg daily, administered in one or two doses.

Dosage for children: The drug is not recommended for children.

4.3 Contra-indications

Daren is contra-indicated in patients who have shown hypersensitivity to the active ingredient or to any of the excipients.

Patients who have a history of angioneurotic edema associated with previous ACE-inhibitor therapy and patients with history of hereditary or idiopathic angioedema.

4.4 Special warnings and special precautions for use

Symptomatic hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving Daren, hypotension is more likely to occur if the patient has been volume depleted, e.g. caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia and decreased renal function. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of Daren and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion. In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Daren. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Daren may be necessary.

Aortic or mitral valve stenosis/Hypertrophic cardiomyopathy

As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction.

Renal function impairment

In cases of renal impairment, hypotension in the beginning of treatment with ACE inhibitors can lead to increased renal impairment in some patients. Acute renal failure has been reported in such cases, and is usually reversible.

Patients with renal impairment may require smaller doses or fewer dosages of Daren. In some patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney, increased blood urea and creatinine have been reported. This is usually reversible when treatment is discontinued and is mainly seen in patients with renal impairment.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when Daren has been given concurrently with a diuretic. Usually, the increases were mild and temporary. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney transplantation

There is no experience regarding the administration of Daren in patients with a recent kidney transplantation. Treatment with Daren is therefore not recommended.

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.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioneurotic oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has rarely been reported in patients treated with ACE inhibitors. This may occur at any time during treatment. In such cases, Daren should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

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

Anaphylactoid reactions during hymenoptera desensitisation

Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL Apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL) apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69[®]) and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Cough

Cough is a common side effect with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Surgery/Anaesthesia

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

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium, (e.g. heparin). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Lithium

The combination of lithium and enalapril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicaments and other forms of interaction

Concomitant use of thiazide diuretics increases the antihypertensive efficacy of enalapril.

The plasma concentration of potassium may increase if enalapril is administered concomitantly with drugs which reduce the excretion of potassium. If it is deemed necessary to give potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes concomitantly, they should be administered carefully and serum potassium should be monitored.

Other antihypertensive agents

Concomitant use of other antihypertensive agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4 Special warnings and special precautions for use).

Tricyclic antidepressants/Antipsychotics/Anaesthetics/Narcotics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 4.4 Special warnings and special precautions for use).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

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.

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

4.6 Pregnancy and lactation

Daren should never be used during pregnancy. Drugs in this group (ACE inhibitors) may cause fetotoxicity during all stages of pregnancy. Exposure to enalapril is known to induce fetotoxicity and neonatal toxicity, i.e. hypotension, renal failure, hyperkalaemia and skull ossification retardation. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. If Daren is used the patient should be made fully aware of possible risk to foetus.

These adverse effects to the embryo and foetus do not seem to occur from intrauterine ACE inhibitor exposure in the first trimester of pregnancy.

In the rare cases where the use of ACE inhibitors is considered vital during pregnancy, repeated ultrasound checks should be made to estimate the condition in the uterus. If oligohydramnios is detected, the treatment with Daren should be stopped unless the treatment is considered vital to the mother. Patient and doctor should be aware that oligohydramnios may not appear until irrevocable damage has occurred with the foetus.

Infants, whose mothers have taken Daren, should be closely monitored for hypotension, oliguria and hyperkalaemia. Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

Enalapril and enalaprilat are excreted into breast milk in very small doses. Daren should not be administered to breast feeding women.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Common (> 1%):

Hypersensitivity: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported.

Cough, dyspnoea, dizziness, headache, depression. Fatigue and asthenia. Hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, abdominal pain, muscle cramps, rash, blurred vision, taste alteration. Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients, chest pain, palpitations, arrhythmia, angina pectoris.

Undesirable effects that have occurred uncommonly or rarely, in clinical comparative studies or during common use of the medicine are:

Blood and the lymphatic system disorders

Anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases.

Metabolism and nutrition disorders

Hypoglycaemia (see 4.4 Special warnings and special precautions for use, Diabetic patients).

Cardiac and vascular disorders

Orthostatic hypotension, Raynaud's phenomenon,

Gastro-intestinal disorders

Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer, stomatitis.

Hepatobiliary disorders

Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis including jaundice.

Nervous system and psychiatric disorders

Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, dream abnormality, sleep disorders.

Respiratory, thoracic and mediastinal disorders

Pulmonary infiltrates, bronchospasm/asthma, rhinitis, pneumonia, dyspnoea, rhinorrhoea, sore throat and hoarseness,

Skin and subcutaneous tissue disorders

Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, erythroderma, pruritus, urticaria, alopecia.

Renal and urinary disorders

Renal dysfunction, renal failure, proteinuria, oliguria.

Other side effects

Impotence, gynecomastia, muscle cramps, flushing, tinnitus, malaise, fever, glossitis.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Investigations

Clinically significant changes to blood value have occurred very rarely with the use of Daren. Increases in blood urea, creatinin, liver enzymes and/or bilirubin have occurred. These increases are usually reversible when treatment with Daren is discontinued. Hyperkalemia and hyponatraemia have been reported.

Decreases in haemoglobin and haematocrit have been reported.

Since the drug was marketed, a few instances of neutropenia, thrombocytopenia, bone marrow depression and agranulocytosis have been reported, where a connection to Daren treatment could not be excluded.

4.9 Overdose

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively.

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. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g. emesis, gastric lavage, administration of absorbents, and sodium sulfate). Enalaprilat may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agent acting on the Renin-Angiotensin system, ACE Inhibitor.

ATC code: C09A A02

Enalapril inhibits the angiotensin converting enzyme (ACE), the enzyme that converts angiotensin I to angiotensin II. Angiotensin II is the most potent vasopressor of the body. Enalapril is a prodrug.

5.2 Pharmacokinetic properties

Approximately 60% of enalapril is absorbed and metabolised in the liver to enalaprilat, which is the active substance. The effects of the drug reach a maximum 4-6 hours after an oral dose and can last for 24 hours. The half-life is about 11 hours but it is much longer if the renal function is impaired. The drug is excreted in the urine.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium *Ph. Eur.*
Lactose monohydrate *Ph. Eur.*
Magnesium stearate *Ph. Eur.*
Pregelatinized maize starch *Ph. Eur.*
Sodium hydrogencarbonate *Ph. Eur.*

In addition the 10 mg and 20 mg tablets contain:
Yellow iron oxide (E172) *U.S.N.F.* and red iron oxide (E172) *U.S.N.F.*

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Daren 2.5 mg: 2 years.
Daren 5 mg: 2 years.
Daren 10 mg: 2 years.
Daren 20 mg: 2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Daren 2.5 mg: PP-container (Securitainer) containing 100 tablets.
Daren 5 mg: PP-container (Securitainer) containing 30 tablets and 100 tablets.
Daren 10 mg: PP-container (Securitainer) containing 30 tablets and 100 tablets.
Daren 20 mg: PP-container (Securitainer) containing 30 tablets and 100 tablets.

6.6 Instructions for use/handling:

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis hf
Reykjavikurvegi 76-78,
220 Hafnarfirdi,
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Daren 2.5 mg: 930016 (IS)
Daren 5 mg: 890085 (IS)
Daren 10 mg: 930017 (IS)
Daren 20 mg: 890086 (IS)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Daren 2.5 mg: 1st January 1994
Daren 5 mg: 1st July 1990
Daren 10 mg: 1st January 1994
Daren 20 mg: 1st July 1990

Renewal of marketing authorisation: 26th February 2004
Duration of Marketing Authorisation: 26th February 2004 – 26th February 2009

10. DATE OF (PARTIAL) REVISION OF THE TEXT

13th July 2004