SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cilaril 1
Cilaril 2.5
Cilaril 5

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mg tablet contains 1 mg of Cilazapril.
Each 2.5 mg tablet contains 2.5 mg of Cilazapril.
Each 5 mg tablet contains 5 mg of Cilazapril.
Excipient(s) with known effect:
Each 1 mg tablet contains 184.4 mg of lactose anhydrous.
Each 2.5 mg tablet contains 183.39 mg of lactose anhydrous.
Each 5 mg tablet contains 181.68 mg of lactose anhydrous.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cilaril 1 is presented as round, biconvex, white film-coated tablets with breakline on one side.

Cilaril 2.5 is presented as round, biconvex, pale salmon-colored film-coated tablets with breakline on one side.

Cilaril 5 is presented as round, biconvex, dark salmon-colored film-coated tablets with breakline on one side.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cilaril is indicated for the treatment of hypertension.

Cilaril is indicated for the treatment of chronic heart failure.

4.2 Posology and method of administration Posology

Cilaril should be administered once daily. As food intake has no clinically significant influence on absorption, Cilaril can be administered before or after a meal. The dose should always be taken at about the same time of day.

Special Dosage Instructions:

Essential hypertension
The recommended initial dosage is 1mg once a day. Dosage should be adjusted individually in accordance with the blood pressure response until control is achieved. Most patients can be maintained on between 2.5 and 5.0mg/day. If the blood pressure

is not adequately controlled with 5mg Cilaril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the anti-hypertensive effect.

Hypertensive patients receiving diuretics
The diuretic should be discontinued two to three days before beginning therapy with Cilaril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. The recommended starting dose in these patients is 0.5mg once daily.

Chronic heart failure
Cilaril can be used as adjunctive therapy with digitalis and/or diuretics in patients with chronic heart failure. Therapy with Cilaril should be initiated with a recommended starting dose of 0.5mg once daily under close medical supervision. The dose should be increased to the lowest maintenance dose of 1mg daily according to tolerability and clinical status. Further titration within the usual maintenance dose of 1mg to 2.5mg daily should be carried out based on patients response, clinical status and tolerability. The usual maximum dose is 5mg once daily.

Results from clinical trials showed that clearance of cilazaprilat in patients with chronic heart failure is correlated with creatinine clearance. Thus in patients with chronic heart failure and impaired renal function special dosage recommendation as given under "Impaired Renal Function" should be followed.

Impaired renal function
Reduced dosages may be required for patients with renal impairment, depending on their creatinine clearance.

The following dose schedules are recommended:

Creatinine clearance	**Initial dose of Cilaril**	**Maximal dose of Cilaril**
> 40ml/min	1mg once daily	5mg once daily
10 - 40ml/min	0.5mg once daily	2.5mg once daily
< 10ml/min	Not recommended	

In patients requiring haemodialysis, Cilaril should be administered on days when dialysis is not performed and the dosage should be adjusted according to blood pressure response.

Elderly
In the treatment of hypertension, Cilaril should be initiated with between 0.5mg and 1mg once daily. Thereafter, the maintenance dose must be adapted to individual response.

In the treatment of chronic heart failure, Cilaril should be initiated with a dose of 0.5mg daily. The maintenance dose of 1mg to 2.5mg must be adapted to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure on high diuretic dosage the recommended starting dose of Cilaril 0.5mg must be strictly followed.

Children
Safety and efficacy in children have not been established therefore there is no recommendation for administration of cilazapril to children.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or any other angiotensin-converting enzyme (ACE) inhibitor
- Hereditary or idiopathic angioneurotic oedema
- History of angioedema associated with previous ACE inhibitors therapy
- Second and third trimesters of pregnancy (see section 4.4 and 4.6)
- The concomitant use of Cilaril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR = 60 ml/min/1.73m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Cilaril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). 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, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic 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 sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication 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 Cilaril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Cilaril may be necessary.

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 section 4.5 and 5.1).

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.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other angiotensin-converting enzyme (ACE) inhibitors, Cilaril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment, the dosage of Cilaril should be adjusted according to creatinine clearance (see section 4.2). Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with Cilaril.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Cilaril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

Proteinuria

In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Cilaril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.*Hypersensitivity/ angiodema*

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Cilaril. This may occur at any time during therapy.

In such cases, Cilaril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. 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.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-l esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain

(see section 4.8).

Anaphylactoid reactions in 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 different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during 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.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

High Cilaril plasma concentrations might occur in patients with impaired hepatic function. Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Cilaril who develop jaundice or marked elevations of hepatic enzymes should discontinue Cilaril 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. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. ACE inhibitors 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 Cilaril 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."

Race

As with other ACE inhibitors, Cilaril may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non- productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery / anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Cilaril may block 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 Cilaril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, or worsening renal function, diabetes mellitus, acute cardiac decompensation, metabolic acidosis, intercurrent events, in particular dehydration, the elderly (age > 70 years) or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, (especially in those with renal impairment, in whom combined use may lead to significant increases in serum potassium), or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned products is deemed appropriate, caution and regular monitoring of serum potassium are recommended (see section 4.5).

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 section 4.5).

Lithium

The combination of lithium and Cilaril is generally not recommended (see section 4.5).

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactose monohydrate content

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other antihypertensive agents
An additive effect may be observed when Cilaril is administered in combination with other antihypertensive agents.

Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with Cilaril. Potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, the combination of Cilaril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent

monitoring of serum potassium.

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Cilaril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of Cilaril.

Angiotensin- receptor antagonists and aliskiren
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 sections 4.3, 4.4 and 5.1).

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 section 4.4).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day
When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (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.

Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Sacubitril/valsartan, racecadotril, mTOR inhibitors and vildagliptin
Based on evidence available, data from literature and likely mechanism regarding the increased risk of angioedema related to pharmacodynamic interactions between angiotensin converting enzyme (ACE) inhibitors and sacubitril/valsartan, racecadotril, mTOR inhibitors and vildagliptin.

Ciclosporin, heparin, trimethoprim and trimethoprim/sulfamethoxazole
Data from literature, the available evidence and likely mechanism suggest that the pharmacodynamic interactions between ACE inhibitors and ciclosporin, heparin, trimethoprim and trimethoprim/sulfamethoxazole resulting in an increased risk of hyperkalaemia are a class effect of ACE inhibitors.

Others
No clinically significant interactions were observed when Cilaril and digoxin,

nitrates, coumarin anticoagulants, and H2 receptor blockers were concomitantly administered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4)

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to an ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Breastfeeding

Because no information is available regarding the use of Cilaril during breastfeeding, Cilaril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

When driving and operating machines, it should be taken into account that occasionally dizziness and fatigue may occur, especially when starting therapy (see sections 4.4 and 4.8).

4.8 Undesirable effects

(a) Summary of the safety profile

The most frequent drug-attributable adverse events observed in patients taking ACE inhibitors are cough, skin rash and renal dysfunction. Cough is more common in women and non-smokers. Where the patient can tolerate the cough, it may be reasonable to continue treatment. In some cases, reducing the dose may help.

Treatment-related adverse events severe enough to stop treatment occur in less than 5% of patients receiving ACE inhibitors.

(b) Tabulated list of adverse reactions

The following list of adverse reactions is derived from clinical trials and post-marketing data in association with Cilaril and/or other ACE inhibitors. Estimates of frequency are based on the proportion of patients reporting each adverse reaction during Cilaril clinical trials that included a total combined population of 7171 patients. Adverse reactions that were not observed during Cilaril clinical trials but have been reported in association with other ACE inhibitors or derived from post-marketing case reports are classified as `rare'.

Frequency categories are as follows: Very Common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000).

System organ class	**Common (>1/100, <1/10)**	**Uncommon (>1/1,000, <1/100)**	**Rare (>1/10,000, <1/1,000)**
Blood and lymphatic system disorders			Neutropenia, agranulocytosis, thrombocytopenia, anemia
Immune system disorders		Angioedema (may involve the face, lips, tongue, larynx or gastrointestinal tract) (see section 4.4)	Anaphylaxis (see section 4.4) Lupus-like syndrome (symptoms may include vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies, increased erythrocyte sedimentation rate, eosinophilia and leukocytosis)
Nervous system disorders	Headache	Dysgeusia	Cerebralischaemia, transient ischaemic attack, ischaemic stroke Peripheral neuropathy
Cardiac disorders		Myocardial ischaemia, angina pectoris, tachycardia, palpitations	Myocardial infarction, arrhythmia
Vascular disorders	Dizziness	Hypotension, Postural hypotension (see section 4.4). Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment.	
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea, bronchospasm, rhinitis	Interstitial lung disease, bronchitis, sinusitis
Gastrointestinal disorders	Nausea	Dry mouth, aphthous stomatitis, decreased appetite, diarrhoea, vomiting	Glossitis, pancreatitis
Hepatobiliary disorders			Abnormal liver function test (including transaminases, bilirubin, alkaline phosphatase, gamma GT) Cholestatic hepatitis with or without necrosis

Skin and subcutaneous tissue disorders		Rash, maculopapular rash	Psoriaform dermatitis, psoriasis (exacerbation), lichen planus, exfoliative dermatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous pemphigoid, pemphigus, Karposi's sarcoma, vasculitis/purpura, photosensitivity reactions, alopecia, onycholysis
Musculoskeletal and connective tissue disorders		Muscle cramps, myalgia, arthralgia	
			Renal impairment, acute renal failure (see section 4.4), blood creatinine increased, blood urea Increased Hyperkalaemia, hyponatraemia, proteinuria, nephrotic syndrome, nephritis.
Reproductive system and breast disorders		Impotence	Gynaecomastia
General disorders and administration site conditions	Fatigue	Excess sweating, flushing, asthenia, sleep disorder	

(c) Description of selected adverse events

Hypotension and postural hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see section 4.4). Renal impairment and acute renal failure are more likely in patients with severe heart failure, renal artery stenosis, pre-existing renal disorders or volume depletion (see section 4.4).

Hyperkalaemia is most likely to occur in patients with renal impairment and those taking potassium sparing diuretics or potassium supplements.

The events of cerebral ischaemia, transient ischaemic attack and ischaemic stroke reported rarely in association with ACE inhibitors may be related to hypotension in patients with underlying cerebrovascular disease. Similarly, myocardial ischaemia may be related to hypotension in patients with underlying ischaemic heart disease.

Headache is a commonly reported adverse event, although the incidence of headache is greater in patients receiving placebo than in those receiving ACE inhibitors.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il/) Additionally, you can report to "Unipharm Ltd".

4.9 Overdose

Symptoms

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Management
The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock. If available, treatment with angiotensin II should be considered.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

If indicated, cilazaprilat, the active form of cilazapril, may be removed from the general irculation by haemodialysis (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09

AA08

Mechanism of action
Cilazapril is a specific, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and thereby the conversion of the inactive angiotensin I to angiotensin II, which is a potent vasoconstrictor. At recommended doses, the effect of Cilazapril in hypertensive patients and in patients with chronic heart failure is maintained for up to 24 hours.

Clinical efficacy and safety
Hypertension
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. It is effective in all degrees of essential hypertension as well as in renal hypertension. The anti-hypertensive effect of Cilaril is usually apparent within the first hour after administration, with maximum effect observed between three and seven hours after dosing. In general, the heart rate (pulse) remains unchanged. Reflex tachycardia is not induced by the drug, although small, clinically insignificant alterations of heart rate may occur. In some patients the anti-hypertensive effect of the drug diminishes toward the end of the dosage interval.

The anti-hypertensive effect of Cilaril is maintained during long-term therapy. No rapid increases in blood pressure have been observed after abrupt withdrawal of Cilaril.

In hypertensive patients with moderate or severe renal impairment, the glomerular filtration rate and renal blood flow remain in general unchanged with Cilaril despite a clinically significant blood pressure reduction.

As with other ACE inhibitors, the blood pressure-lowering effect of Cilaril in Black patients may be less pronounced than in non-Blacks. However, racial differences in response are no longer evident when Cilaril is administered in combination with hydrochlorothiazide.

Chronic heart failure
No clinical trials have been carried out which prove the effect of Cilaril on morbidity and mortality in heart failure.

In patients with chronic heart failure, the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally activated, leading to enhanced

systemic vasoconstriction and to the promotion of sodium and water retention. By suppressing the renin-angiotensin-aldosterone system, Cilaril improves loading conditions in the failing heart by reducing systemic vascular resistance (afterload) and pulmonary capillary wedge pressure (preload) in patients on diuretics and/or digitalis.

Furthermore, the exercise tolerance of these patients increases significantly thus showing an improvement in quality of life. The haemodynamic and clinical effects occur promptly and persist.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affair Nephropathy in Diabetes) have examined the use of combination of an ACE-inhibitor with angiotensin II receptor blocker. ONTARGET was a study

conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/ or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmaodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. CV death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

The concomitant use of aliskiren with an ACE-inhibitor or an angiotensin II receptor blocker is contraindicated in patients with type 2 diabetes mellitus or renal impairment (GFR =60ml/min/1.73m2).

5.2 Pharmacokinetic properties

Absorption

Cilazapril is efficiently absorbed and rapidly converted to the active form, Cilazaprilat. Ingestion of food immediately prior to Cilaril administration, delays and reduces the absorption to a minor extent which, however, is therapeutically irrelevant. The bioavailability of Cilazaprilat after oral administration of Cilaril approximates 60% based on urinary recovery data. Maximum serum concentrations are reached within two hours after drug administration and are directly related to dosage.

Elimination

Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of nine hours after once-daily dosing with Cilaril.

Special populations

Renal impairment

In patients with renal impairment, higher plasma concentrations of Cilazaprilat are observed than in patients with normal renal function, since drug clearance is reduced when creatinine clearance is lower. There is no elimination in patients with complete renal failure, but haemodialysis reduces concentrations of

Cilazapril and Cilazaprilat to a limited extent.

Elderly
In elderly patients whose renal function is normal for age, plasma concentrations of Cilazaprilat may be up to 40% higher and the clearance up to 20% lower than in

younger patients. Similar changes in the pharmacokinetics occur in patients with moderate to severe liver cirrhosis.

Chronic heart failure
In patients with chronic heart failure the clearance of Cilazaprilat is correlated with the creatinine clearance. Thus, dosage adjustments do not go beyond those recommended for patients with impaired renal functions (see section 4.2) should not be necessary.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

In fertility and general reproduction performance testing in rats, dosing with 50 mg/kg/day of Cilaril resulted in greater implantation losses, less viable fetuses, smaller pups, and dilatation of the renal pelvis in the pups. No teratogenic effects or adverse effects on post-natal pup development were observed in rats and Cynomolgus monkeys during embryotoxicity testing. In the rats, however, at a dose of 400 mg/kg/day, renal cavitation was observed in the pups. In peri- and post-natal toxicity testing in rats, dosing with 50 mg/kg/day resulted in greater pup mortality, smaller pups, and delayed unfolding of the pinna. On administration of 14C-CILAZAPRIL to pregnant mice, rats and monkeys, radioactivity was measured in the foetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and post-natal mortality have been observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cilaril 1:
Lactose anhydrous, Maize starch, Hydroxypropyl methylcellulose, Sodium stearyl fumarate, Coating blend white (HPMC, Titanium dioxide, Polyethylene glycol).
Cilaril 2.5; 5:
Lactose anhydrous, Maize starch, Hydroxypropyl methylcellulose, Sodium stearyl fumarate, Coating blend white (HPMC, Titanium dioxide, Polyethylene glycol), Coating blend brown (HPMC, Talc, Polyethylene glycol, Iron oxide yellow, Titanium dioxide, Iron oxide red, Iron oxide black), Coating blend red (HPMC, Titanium dioxide, Polyethylene glycol, Erythrosine aluminium lake, Quinoline yellow aluminium lake).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store at a temperature below 25°C, and in a place protected from light

6.5 Nature and contents of container

Aluminium/Aluminium blister packed of 7,10,14,15,28,30 Tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 Marketing authorisation holder

License Holder: Unipharm ltd, 1 Shevet Shimon St. P.O. Box 16545, 6116401, Tel Aviv, Israel

Manufacturer: Unipharm Ltd., "Mevo Carmel" Industrial Park

8 Marketing authorisation number(s)

Cilaril 1: 136 01 31495 00
Cilaril 2.5: 135 93 31305 00
Cilaril 5: 135 94 31282 00

Revised in January 2026