

## Data Sheet

# Arrow - Cilazapril

*cilazapril monohydrate 1 mg, 2.5 mg and 5 mg tablets*

## Name of Medicine

Cilazapril monohydrate is a white to almost white crystalline powder. It is slightly soluble in water, freely soluble in methanol and in methylene chloride. The molecular formula is  $C_{22}H_{31}N_3O_5 \cdot H_2O$ , molecular mass is 435.5 and CAS number is 92077-78-6.

## Presentation

Arrow - Cilazapril 1 mg tablets are film-coated, yellow oval-shaped, biconvex tablet with "CL | 1" on one side and ">" on the other side.

Arrow - Cilazapril 2.5 mg tablets are film-coated, pinkish-brown oval-shaped, biconvex tablet with "CL | 2" on one side and ">" on the other side.

Arrow - Cilazapril 5 mg tablets are film-coated, reddish-brown oval-shaped, biconvex tablet with "CL | 3" on one side and ">" on the other side.

## Uses

### ***Actions***

Cilazapril is a specific, long-acting 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 congestive heart failure is maintained for up to 24 hours.

In patients with normal renal function, serum potassium usually remains within the normal range during cilazapril treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise (see Warnings and precautions - *Serum potassium*; Interactions).

### ***Efficacy***

#### **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 antihypertensive effect of cilazapril is usually apparent within the first hour after administration, with maximum effect observed between 3 and 7 hours after dosing. In general, the heart rate remains unchanged. Reflex tachycardia is not induced, although small, clinically insignificant alterations of heart rate may occur. In some patients blood pressure reduction may diminish towards the end of the dosage interval. The antihypertensive effect of cilazapril is maintained during long-term therapy. No rapid increase in blood pressure has been observed after abrupt withdrawal of cilazapril.

In hypertensive patients with moderate to severe renal impairment, the glomerular filtration rate and renal blood flow generally remained unchanged with cilazapril, despite a clinically significant blood pressure reduction.

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

### **Congestive heart failure**

In patients with congestive heart failure, the renin-angiotensin-aldosterone and sympathetic nervous systems are generally activated, leading to enhanced systemic vasoconstriction and promotion of sodium and water retention. By suppressing the renin-angiotensin-aldosterone system, cilazapril 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, showing an improvement in quality of life. The haemodynamic and clinical effects occur promptly and persist.

### ***Pharmacokinetics***

Cilazapril is efficiently absorbed and rapidly converted to the active form, cilazaprilat. Ingestion of food immediately prior to cilazapril administration delays and reduces absorption to a minor extent which, however, is therapeutically irrelevant. The bioavailability of cilazaprilat from oral cilazapril approximates 60%, based on urinary recovery data. Maximum plasma concentrations are reached within 2 hours after administration and are directly related to dosage.

Cilazapril is eliminated unchanged by the kidneys, with an "effective" half-life of 9 hours after once-daily dosing with cilazapril.

### **Pharmacokinetics in special populations**

*Renal impairment:* In patients with renal impairment, higher plasma concentrations of cilazaprilat are observed than in patients with normal renal function, since clearance is reduced when creatinine clearance is lower. There is no elimination in patients with complete renal failure, but

haemodialysis reduces concentrations of both cilazapril and cilazaprilat to a limited extent.

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

*Hepatic impairment:* In patients with liver cirrhosis increased plasma concentrations and reduced plasma and renal clearance were observed, with a greater effect on cilazapril than on its active metabolite cilazaprilat.

*Congestive heart failure:* In patients with congestive heart failure, clearance of cilazaprilat is correlated with creatinine clearance. Thus, dosage adjustments beyond those recommended for patients with impaired renal function (see *Special dosage instructions*) should not be necessary.

## Indications

Cilazapril is indicated in the treatment of all grades of essential hypertension and renovascular hypertension. cilazapril is also indicated in the treatment of congestive heart failure as an adjunctive therapy with digitalis and/or diuretics.

## Dosage and Administration

### Standard dosage

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

Arrow – Cilazapril 1 mg tablet can be halved to provide a 0.5 mg dose.

Arrow – Cilazapril is not available for the lower dose of 0.25 mg. If a dose of 0.25 mg of cilazapril is required, an alternative product must be used.

### Special dosage instructions

#### *Essential hypertension*

The recommended initial dosage is half a 2.5 mg tablet once a day. Blood pressure should be assessed, and dosage adjusted individually in accordance with the blood pressure response. The usual dose range of cilazapril is 2.5 – 5 mg once daily. If blood pressure is not adequately controlled with 5 mg cilazapril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the antihypertensive effect.

#### *Renovascular hypertension*

Treatment with cilazapril should be initiated with a dose of 0.5 mg or 0.25 mg once daily since these patients may experience more pronounced decreases

in blood pressure in response to ACE inhibitors than patients with essential hypertension. The maintenance dose should be adjusted individually.

### ***Hypertensive patients receiving diuretics***

The diuretic should be discontinued 2-3 days before beginning therapy with cilazapril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. The recommended starting dose in these patients is 0.5 mg once daily.

### ***Congestive heart failure***

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

Results from clinical trials showed that clearance of cilazaprilat was correlated with creatinine clearance in patients with congestive heart failure. The special dosage recommendation should thus be followed in congestive heart failure patients with impaired renal function (see Special dosage instructions - *Patients with renal impairment*).

### ***Patients with renal impairment***

Reduced dosages may be required for patients with renal impairment, depending on their creatinine clearance (see Warnings and precautions, *Haemodialysis/anaphylaxis*). The following dosage schedules are recommended:

<b>Creatinine Clearance</b>	<b>Initial dose of cilazapril</b>	<b>Maximal dose of cilazapril</b>
> 40 ml/min	1 mg once daily	5 mg once daily
10-40 ml/min	0.5 mg once daily	2.5 mg once daily
< 10 ml/min	0.25 - 0.5 mg once or twice a week according to blood pressure response	

### ***Liver cirrhosis***

In the unlikely event that patients with liver cirrhosis should require treatment with cilazapril, it should be initiated with caution at a dose of 0.5 mg or less once daily, because significant hypotension may occur.

### ***Elderly patients with hypertension***

Treatment with cilazapril should be initiated with 0.5 mg once daily. Thereafter, the maintenance dose of 1 mg to 2.5 mg must be adapted to individual tolerability, response and clinical status.

### ***Elderly patients with congestive heart failure***

The recommended starting dose of cilazapril 0.5 mg must be strictly followed in elderly patients with congestive heart failure receiving high-dose diuretic.

### ***Children***

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

## **Contraindications**

Cilazapril is contraindicated in patients with known hypersensitivity to cilazapril, to any component of the product or to other ACE inhibitors.

Like other ACE inhibitors, cilazapril is contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Cilazapril, like other ACE inhibitors, is contraindicated during pregnancy and lactation (see Pregnancy, nursing mothers).

## **Warnings and Precautions**

Like other ACE inhibitors, cilazapril should be used with caution in patients with aortic stenosis or outflow obstruction.

The recommended starting dose of cilazapril 0.5 mg must be strictly followed in elderly patients with congestive heart failure receiving high-dose diuretic.

### **Neutropenia**

Neutropenia and agranulocytosis have been rarely reported with ACE inhibitors. Periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease and renal disease such as systemic lupus erythematosus and scleroderma, or in patients receiving immunosuppressive therapy, especially when they also have impaired renal function.

### **Symptomatic hypotension**

Occasionally, symptomatic hypotension has been reported with ACE inhibitor therapy, particularly in patients with sodium or volume depletion in connection with conditions such as vomiting or diarrhea, pretreatment with diuretics, low-sodium diet or after dialysis.

Acute hypotension should be treated by having the patient rest in the supine position and may require infusion of normal saline or volume expanders. After volume repletion, cilazapril therapy may be continued. However, if symptoms persist, the dosage should be reduced or the medicine discontinued.

Patients with congestive heart failure may experience a pronounced blood pressure decrease in response to ACE inhibitors. However, no symptomatic hypotension was observed in clinical trials following the first dose of 0.5 mg cilazapril in patients with congestive heart failure.

See *Special dosage instructions* - Patients with renal impairment.

### **Renal impairment**

Reduced dosages may be required for patients with renal impairment, depending on their creatinine clearance (see *Special dosage instructions*). Treatment with ACE inhibitors may produce increases in blood urea nitrogen and/or serum creatinine. Although these alterations are usually reversible upon discontinuation of cilazapril and/or diuretic therapy, cases of severe renal dysfunction and, rarely, acute renal failure have been reported.

In this patient population, renal function should be monitored during the first weeks of therapy.

### **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.

### **Serum potassium**

Concomitant administration of potassium-sparing diuretics or potassium supplements may lead to increases in serum potassium, particularly in patients with renal impairment. Therefore, if concomitant use of such agents is indicated, their dosage should be reduced when cilazapril is initiated, and serum potassium and renal function should be monitored carefully (see *Properties and effects - Mechanism of action; Interactions*).

### **Surgery/anaesthesia**

The use of ACE inhibitors in combination with anaesthetic medicines in surgery that also have blood pressure-lowering effects can produce arterial hypotension. If this occurs, volume expansion by means of intravenous infusion or - if resistant to these measures - angiotensin II infusion is indicated.

## **Hypersensitivity/angioneurotic oedema**

Angioneurotic oedema has been reported in patients being treated with ACE inhibitors.

## **Haemodialysis/anaphylaxis**

Although the mechanism involved has not been definitely established, there is clinical evidence that haemodialysis or haemofiltration with polyacrylonitrile methallyl sulfate high-flux membranes (e.g. AN69) or LDL apheresis, if performed in patients being treated with ACE inhibitors, including cilazapril, can lead to the provocation of anaphylaxis/anaphylactoid reactions including life-threatening shock. The above-mentioned procedures must therefore be avoided in such patients.

Anaphylactic reactions can also occur in patients undergoing desensitisation therapy with wasp or bee venom while receiving an ACE inhibitor. cilazapril must therefore be interrupted before the start of desensitization therapy. Additionally, cilazapril must not be replaced by a beta blocker in this situation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **Diabetes**

Administration of ACE inhibitors in patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycaemic agents or insulin.

## **Dual blockade of the renin-angiotensin-aldosterone system**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

## ***Ability to Drive and Use Machines***

As with other ACE inhibitors, impairment of performance in activities requiring complete mental alertness (e.g. driving a motor vehicle) is not to be expected with cilazapril. However, it should be noted that dizziness may occasionally occur (see Adverse Effects - Post Marketing).

## ***Pregnancy, nursing mothers***

Foetotoxicity has been observed for ACE inhibitors in animals. Although there is no specific experience with cilazapril, use of ACE inhibitors in human pregnancy has been associated with oligohydramnios, intrauterine growth restriction, neonatal hypotension, anuria and renal tubular dysplasia.

In addition, foetal exposure to ACE inhibitors during the first trimester of pregnancy has been associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly, spina bifida) and also an increased risk of kidney malformations.

Pregnant women should be informed of the potential hazards to the foetus and must not take cilazapril during pregnancy (see Contraindications).

It is not known whether cilazapril passes into human breast milk, but since animal data show the presence of cilazaprilat in rat milk, cilazapril must not be administered to nursing mothers (see Contraindications).

## **Adverse Effects**

Headache and dizziness are the most frequently reported events in patients taking cilazapril for hypertension. In congestive heart failure clinical trials, dizziness and coughing were the most frequently reported events in patients taking cilazapril.

### **Post Marketing**

Cilazapril is usually well tolerated. In most cases, side effects are transient, mild or moderate in degree, and do not require discontinuation of therapy. The most common adverse effects include dry cough, rash, hypotension, dizziness, fatigue, headache, and nausea, dyspepsia and other gastrointestinal disturbances.

*Blood and lymphatic system disorders:* Blood disorders have been reported with ACE inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia and anaemia.

*Cardiac disorders:* Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume-depleted patients. Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations and chest pain.

*Gastrointestinal disorders:* As for other ACE inhibitors, isolated cases of pancreatitis, in some cases fatal, have been reported in patients treated with cilazapril.

*Hepatobiliary disorders:* Single cases of liver function disorders, such as increased liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis, have been reported.

*Immune system disorders:* As with other ACE inhibitors, angioneurotic oedema has been reported, although rarely, in patients receiving cilazapril. Angioedema involving the tongue, glottis or larynx may be fatal. Since this syndrome can be associated with laryngeal oedema, cilazapril should be discontinued and appropriate therapy instituted without delay when involvement of the face, lips, tongue, glottis and/or larynx occurs. Emergency therapy should be given including, but not necessarily limited to, immediate intramuscular adrenalin (epinephrine) solution 1:1000 (0.3 to 0.5ml) or slow intravenous adrenalin 1mg/ml (observing dilution instructions) with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

*Skin and subcutaneous tissue disorders:* Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photo-sensitivity, alopecia, and other hypersensitivity reactions have also been reported.

*Renal and urinary disorders:* Isolated cases of acute renal failure have been reported in patients with severe heart failure, renal artery stenosis or renal disorders (see Warnings and precautions - *Renal impairment*).

### **Laboratory test findings**

Clinically relevant changes in laboratory test values possibly or probably related to cilazapril treatment have been observed only rarely.

Minor, mostly reversible increases in serum creatinine/urea have been observed in patients treated with cilazapril. Such changes are likely to occur in patients with renal artery stenosis or renal impairment (see Warnings and precautions - *Renal impairment*), but they have also occasionally been observed in patients with normal renal function, particularly in those receiving concomitant diuretics.

## **Interactions**

Lithium should generally not be given with ACE inhibitors. ACE inhibitors reduce the renal clearance of lithium and add a risk of lithium toxicity.

An additive effect may be observed when cilazapril is administered in combination with other blood pressure-lowering agents.

Potassium-sparing diuretics or potassium supplements administered together with cilazapril can lead to increases in serum potassium, particularly in patients with renal impairment (see Uses - *Action*; Warnings and Precautions).

As with other ACE inhibitors, use of cilazapril concomitantly with a non-steroidal anti-inflammatory (NSAID) may diminish the antihypertensive effect of cilazapril. This does not appear to occur in patients treated with cilazapril prior to the administration of NSAIDs.

There was no increase in digoxin plasma concentrations when cilazapril was administered concomitantly with digoxin. Furthermore, no clinically significant interactions were observed when cilazapril was administered concomitantly with nitrates, coumarin anticoagulants and H<sub>2</sub>-receptor blockers. No significant pharmacokinetic interactions between cilazapril and frusemide or thiazides were noted.

## **Overdosage**

While single doses of up to 160 mg cilazapril have been administered to normal healthy volunteers without untoward effects on blood pressure, only very few data on overdose are available in patients. The most likely manifestations are hypotension, which may be severe, hyperkalaemia, hyponatraemia and renal impairment with metabolic acidosis. Treatment should be mainly symptomatic and supportive. If indicated, cilazaprilat, the active form of cilazapril, can be partially removed from the body by haemodialysis. Specific therapy with angiotensinamide may be considered if conventional therapy is ineffective.

## **Pharmaceutical Precautions**

Store below 25 °C.

## **Medicine Classification**

Prescription Medicine

## **Package Quantities**

Arrow – Cilazapril 1 mg, 2.5 mg and 5 mg tablets are available in blister packs of 30 tablets, and bottle packs of 100 and 500 tablets.

## **Name and Address**

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## **Date of Preparation**

27 September 2011