

# Data Sheet

## Inhibace<sup>®</sup>

*Cilazapril 0.5 mg, 2.5 mg and 5 mg tablets*

**Angiotensin-Converting Enzyme (ACE) inhibitor**

---

## Composition

---

### Active ingredient

cilazapril

Tablets 0.5 mg, 2.5 mg and 5 mg.

### Excipients

*Kernel:*

Lactose monohydrate, maize starch, hypromellose, purified talc, sodium stearyl fumarate. (See Warnings and precautions for a warning concerning lactose.)

*Film-coating:*

Hypromellose, purified talc, titanium dioxide (E171).

The 2.5 mg and 5 mg tablets also have red iron oxide (E172).

The 2.5 mg tablet has in addition yellow iron oxide (E172).

### Appearance

Inhibace 0.5 mg tablets are film-coated, white and oval with bevelled edges. They measure 10 mm by 5 mm and have "CIL 0.5" on one side and a break bar on the other side.

Inhibace 2.5 mg tablets are film-coated, pink and oval with bevelled edges. They measure 12 mm by 6mm and have "CIL 2.5" on one side and a break bar on the other side.

Inhibace 5 mg tablets are film-coated, reddish-brown and oval with bevelled edges. They measure 11 mm by 6 mm and have "CIL 5" on one side and a break bar on the other side.

---

## Properties and effects

---

### Mechanism of action

Inhibace 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 Inhibace 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 Inhibace treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise (see Warnings and precautions – *Serum potassium*; Interactions).

## **Efficacy**

### ***Hypertension***

Inhibace 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 Inhibace 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 Inhibace is maintained during long-term therapy. No rapid increase in blood pressure has been observed after abrupt withdrawal of Inhibace.

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

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

Cilazaprilat is eliminated unchanged by the kidneys, with an “effective” half-life of 9 hours after once-daily dosing with Inhibace.

### 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 Dosage and Administration - *Special dosage instructions*) should not be necessary.

---

## Indications

---

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

---

## Dosage and Administration

---

### Standard dosage

Inhibace should be administered once daily. As food intake has no clinically significant influence on absorption, Inhibace 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 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 Inhibace is 2.5 - 5 mg once daily. If blood pressure is not adequately controlled with 5 mg Inhibace once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the antihypertensive effect.

#### ***Renovascular hypertension***

Treatment with Inhibace 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 Inhibace 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***

Inhibace can be used as adjunctive therapy with digitalis and/or diuretics in patients with congestive heart failure. Therapy with Inhibace 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 Inhibace</b>	<b>Maximal dose of Inhibace</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 Inhibace 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 Inhibace 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**

---

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

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

Inhibace, like other ACE inhibitors, is contraindicated during pregnancy and lactation (see Warnings and precautions - *Pregnancy, nursing mothers*).

---

## Warnings and precautions

---

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

The recommended starting dose of Inhibace 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, Inhibace 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 Inhibace 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 Dosage and Administration - *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 Inhibace 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 Inhibace 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**

The combination of an ACE inhibitor other than cilazapril and an angiotensin receptor antagonist elicited only a marginal incremental drop in blood pressure as compared to monotherapy. As a consequence of inhibiting the renin-angiotensin-aldosterone system an increased risk of developing adverse events was observed in susceptible individuals, including worsening of renal failure, hypotension and hyperkalaemia. Based on these results dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an angiotensin-receptor antagonist to cilazapril) is not recommended. If still considered necessary it 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 Inhibace. However, it should be noted that dizziness may occasionally occur (see Undesirable Effects – *Post Marketing*).

### **Pregnancy, nursing mothers**

Foetotoxicity has been observed for ACE inhibitors in animals. Although there is no specific experience with Inhibace, 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 Inhibace 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, Inhibace must not be administered to nursing mothers (see Contraindications).

---

## Undesirable Effects

---

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

### Post Marketing

Inhibace 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 Inhibace.

*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 Inhibace. Angioedema involving the tongue, glottis or larynx may be fatal. Since this syndrome can be associated with laryngeal oedema, Inhibace 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 0.5 mL) 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 Inhibace treatment have been observed only rarely.

Minor, mostly reversible increases in serum creatinine/urea have been observed in patients treated with Inhibace. 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 Inhibace is administered in combination with other blood pressure-lowering agents.

Potassium-sparing diuretics or potassium supplements administered together with Inhibace can lead to increases in serum potassium, particularly in patients with renal impairment (see Properties and Effects – *Mechanism of Action*; Warnings and precautions).

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

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

---

## Overdosage

---

While single doses of up to 160 mg Inhibace 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 Inhibace, can be partially removed from the body by haemodialysis. Specific therapy with angiotensinamide may be considered if conventional therapy is ineffective.

---

## Stability

---

Store below 25 °C.

This medicine should be used before the expiry date shown on the pack.

Keep out of reach of children.

---

## Medicine Classification

---

Prescription Medicine

---

## Packs

---

0.5 mg tablets: packs of 30

2.5 mg tablets: packs of 28

5.0 mg tablets: packs of 28



---

## **Name and Address**

---

Roche Products (New Zealand) Limited  
PO Box 12492, Penrose  
Auckland 1642

Customer enquiries: 0800 656 464

---

## **Date of Preparation**

---

14 January 2011