

NEW ZEALAND DATA SHEET

ZAPRIL



1. Product Name

ZAPRIL, 0.5 mg, 2.5 mg, 5 mg, film coated tablets.

2. Qualitative and Quantitative Composition

Each ZAPRIL tablet contains 0.5 mg, 2 mg or 5 mg of cilazapril as cilazapril monohydrate.

ZAPRIL tablets contain lactose. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

ZAPRIL 0.5 mg tablets are white, oval-shaped, biconvex, film coated tablets, with "CI" scoreline "0.5" on one side and "G" on the other side. Each tablet contains 0.5 mg cilazapril.

ZAPRIL 2.5 mg tablets are pinkish brown, oval-shaped, biconvex, film coated tablets, with "CI" scoreline "2.5" on one side and "G" on the other side. Each tablet contains 2.5 mg cilazapril.

ZAPRIL 5 mg tablets are reddish brown, oval-shaped, biconvex, film coated tablets, with "CI" scoreline "5" on one side and "G" on the other side. Each tablet contains 5 mg cilazapril.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 *Therapeutic indications*

ZAPRIL is indicated in the treatment of all grades of essential hypertension and renovascular hypertension.

ZAPRIL is also indicated in the treatment of congestive heart failure as an adjunctive therapy with digitalis and/or diuretics.

4.2 *Dose and method of administration*

Dose

Essential hypertension

The recommended initial dosage is half a 2.5mg 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 to 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 to 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 to 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 in Special population section should thus be followed in congestive heart failure patients with impaired renal function.

Special populations

Renal impairment

Reduced dosages may be required for patients with renal impairment, depending on their creatinine clearance (see also section 4.4). The following dosage schedules are recommended:

Creatinine Clearance	Initial dose of cilazapril	Maximal dose of cilazapril
>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 to 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 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 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.

Paediatric

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

Method of administration

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

4.3 Contraindications

ZAPRIL is contraindicated in patients with known hypersensitivity to cilazapril, to any component of the product or to other ACE inhibitors. For details of the components see section 6.1.

ZAPRIL is contraindicated in patients with a history of angioedema associated with previous ACE inhibitor therapy.

Concomitant use with sacubitril/valsartan therapy is contraindicated. Cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see section 4.4 and 4.5).

ZAPRIL, is contraindicated during the second and third trimesters of pregnancy (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

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 antihypertensive 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 section 4.3 and 4.6)

Hypotension

ACE inhibitors may cause severe hypotension, especially when starting treatment. First-dose hypotension is most likely to occur in patients whose renin-angiotensin-aldosterone system is activated, such as in renovascular hypertension or other causes of renal hypoperfusion, sodium or volume depletion, or previous treatment with other vasodilators. These conditions can co-exist, particularly in severe heart failure.

Hypotension should be treated by placing the patient supine and volume expansion. Cilazapril may be continued once the patient is volume replete, but should be given at a lower dose or discontinued if the hypotension persists.

At-risk patients should start treatment with cilazapril under medical supervision, with a low initial dose and careful titration. If possible, diuretic therapy should be discontinued temporarily.

Similar caution should be taken for patients with angina pectoris or cerebrovascular disease, in whom hypotension can cause myocardial or cerebral ischaemia.

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.

Renal impairment

In patients with renal impairment, the dosage of cilazapril 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.

ACE inhibitors have established renoprotective effects, but can cause reversible impairment of renal function in the setting of reduced renal perfusion, whether due to bilateral renal artery stenosis, severe congestive heart failure, volume depletion, hyponatraemia or high dosages of diuretics, and in those receiving treatment with NSAIDs. Preventive measures include withdrawing or temporarily withholding diuretics, beginning therapy with very small doses of ACE inhibitors, and cautious dose titration.

In patients with renal artery stenosis, activation of the renin-angiotensin-aldosterone system helps to maintain renal perfusion by causing constriction of the efferent arteriole. Hence, blockade of angiotensin II formation, and possibly also an increase in the formation of bradykinin, causes efferent arteriolar vasodilation resulting in a reduction in glomerular filtration pressure. Hypotension contributes further to a reduction in renal perfusion (see section 4.4). As with other agents acting on the renin-angiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with cilazapril. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Hypersensitivity/angioedema

Angioedema has been associated with ACE inhibitors, with a reported incidence of 0.1-0.5%. Angioedema due to ACE inhibitors can present as recurrent episodes of facial swelling, which resolves on withdrawal, or as acute oropharyngeal edema and airways obstruction, which requires emergency treatment, and may be life-threatening. A variant form is angioedema of the intestine, which tends to occur within the first 24-48 hours of treatment. The risk of angioedema appears to be greater in black-skinned than non black-skinned patients. Patients with a history of angioedema unrelated to ACE inhibitors may be at greater risk.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of cilazapril. Treatment with cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see section 4.3 and 4.5).

Concomitant use of ACE inhibitor with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylaxis

Haemodialysis

Anaphylaxis has occurred in patients dialysed with high flux membranes (e.g. AN 69) receiving ACE inhibitors. Consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent in such patients.

Low-density lipoproteins (LDL) apheresis

Patients receiving ACE inhibitors during LDL apheresis with dextran sulfate have experienced life-threatening anaphylaxis. This can be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitization

Anaphylactic reactions can also occur in patients undergoing desensitization therapy with wasp or bee venom while receiving an ACE inhibitor. Cilazapril must be stopped before the start of desensitization therapy, and should not be replaced by a beta blocker.

Hepatic disorders

Single cases of liver function disorders, such as increased values of liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis have been reported. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue the cilazapril and receive appropriate medical follow-up. In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, cilazapril should be initiated at a lower dose and with great caution because significant hypotension may occur (see section 4.2). In patients with ascites, cilazapril administration is not recommended.

Neutropenia

Rarely, neutropenia and agranulocytosis have been associated with ACE inhibitors, especially in patients with renal failure or collagen vascular disease and those receiving immunosuppressive therapy. Periodic monitoring of leukocyte count is recommended in such patients.

Serum potassium

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Diabetes

Administration of ACE inhibitors to patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycemic agents or insulin, especially in patients with renal impairment. In such patients, glucose levels should be carefully monitored during initiation of treatment with an ACE inhibitor.

Surgery/anaesthesia

Anaesthetic agents with blood pressure lowering effects can cause hypotension in patients receiving ACE inhibitors. Hypotension in this setting can be corrected with volume expansion.

Aortic stenosis/hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patients with obstructive cardiac disorders (e.g. mitral stenosis, aortic stenosis, hypertrophic cardiomyopathy), since cardiac output cannot increase to compensate for systemic vasodilation, and there is a risk of severe hypotension.

Ethnicity

ACE inhibitors are less effective as antihypertensives in patients with black skin colour. These patients also have a higher risk of angioedema.

Lactose intolerance

Owing to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines 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 risk of lithium toxicity with ACE inhibitors.

Use of cilazapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Other antihypertensive agents

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalemia may occur in some patients treated with cilazapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when cilazapril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of cilazapril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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 cilazapril (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 cilazapril.

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 aspirin a 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 medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-

lowering effect with risk of hypoglycemia. 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.

Medicines increasing the risk of angioedema

Sacubitril/valsartan

The concomitant use of cilazapril with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Others

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (see section 4.4).

Others

No clinically significant interactions were observed when cilazapril and digoxin, nitrates, coumarin anticoagulants, and H₂ receptor blockers were concomitantly administered.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors such as cilazapril is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors such as cilazapril is contraindicated during the second and third trimester of pregnancy (see section 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 antihypertensive 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia) (see section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound examination of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see section 4.3 and 4.4).

Breastfeeding

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

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

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 section 4.4 and 4.8).

4.8 Undesirable effects

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.

Tabulated list of adverse reactions

The following list of adverse reactions is derived from clinical trials and post-marketing data in association with cilazapril and/or other ACE inhibitors. Estimates of frequency are based on the proportion of patients reporting each adverse reaction during cilazapril clinical trials that included a total combined population of 7171 patients. Adverse reactions that were not observed during cilazapril 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 and < 1/10
Uncommon:	≥ 1/1000 and < 1/100
Rare:	< 1/1000

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	Cerebral ischaemia, 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, Kaposi's sarcoma, vasculitis/purpura, photosensitivity reactions, alopecia, onycholysis
Musculoskeletal and connective tissue disorders		Muscle cramps, myalgia, arthralgia	

Renal and urinary disorders			Renal impairment, acute renal failure (see section 4.4), blood creatinine increased, blood urea increased Hyperkalemia, hyponatremia, proteinuria, nephrotic syndrome, nephritis
Reproductive system and breast disorders		Impotence	Gynaecomastia
General disorders and administration site conditions	Fatigue	Excess sweating, flushing, asthenia, sleep disorder	

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).

Hyperkalemia 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) 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.

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 circulation by haemodialysis (see section 4.4).

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: ACE inhibitor, ATC code: C09AA08

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 congestive 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 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

No clinical trials have been carried out which prove the effect of cilazapril on morbidity and mortality in 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.

5.2 *Pharmacokinetic properties*

Absorption

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.

Elimination

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

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

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 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 general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. Pharmaceutical Particulars

6.1 List of excipients

This product also contains:

- corn starch
- lactose
- sodium bicarbonate
- colloidal silicon dioxide
- sodium stearyl fumarate
- titanium dioxide
- triacetin
- hypromellose (0.5 mg)
- red iron oxide (2.5 mg)
- yellow iron oxide (2.5 mg)

- hydroxypropylmethylcellulose (2.5 mg, 5 mg)
- polydextrose (2.5 mg, 5 mg)
- macrogol (2.5 mg, 5 mg)
- sunset yellow (5 mg)
- indigo carmine aluminium lake blue (5 mg)
- D&C Yellow 10 (5 mg)
- FD&C Red 40 (5 mg)

ZAPRIL is gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Pack type

HDPE bottle with a polypropylene closure and a silica gel desiccant.

Blister pack, OPA/Al/PVC-Al.

Pack size

0.5 mg tablets: bottles of 30 and 90 tablets

2.5 mg tablets: blister packs of 30 and 90 tablets, bottles of 90 tablets

5 mg tablets: blister packs of 30 and 90 tablets, bottles of 90 tablets

Not all pack type or sizes may be marketed

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11-183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

19 November 2009

10. Date of Revision of the Text

18 June 2019

Summary table of changes

Section	Summary of new information
4.3	Cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
4.4	Moved Sacubitril/valsartan warning under Hypersensitivity/angioedema and replaced neprilysin (NEP) with specific molecules. Warning on hyperkalemia in patients taking trimethoprim, co-trimoxazole and angiotensin-receptor blockers
4.5	Replaced neprilysin (NEP) with specific molecules. Added interaction with trimethoprim, co-trimoxazole, ciclosporin and heparin.