New Zealand Data Sheet

APO-CILAZAPRIL

1. APO-CILAZAPRIL (1mg, 2.5mg & 5mg film coated tablets)
   APO-CILAZAPRIL 1mg film coated tablets
   APO-CILAZAPRIL 2.5mg film coated tablets
   APO-CILAZAPRIL 5mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cilazapril monohydrate 1.0425mg (equivalent to Cilazapril 1mg)
Cilazapril monohydrate 2.606mg (equivalent to Cilazapril 2.5mg)
Cilazapril monohydrate 5.213mg (equivalent to Cilazapril 5mg)

Chemical Structure:

\[
\text{Molecular Formula: } C_{22}H_{31}N_{3}O_{5}\cdot H_{2}O
\]

Molecular Mass: 435.50

Excipient(s) with known effect

APO-CILAZAPRIL contains corn starch.

APO-CILAZAPRIL is gluten free and lactose free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

1mg APO-CILAZAPRIL Yellow, oval, biconvex, film coated tablet. Engraved “CZ” over European bisect “1” on one side, “APO” on the other side. Each tablet typically weighs 82mg

2.5mg APO-CILAZAPRIL Dusty rose, oval, biconvex, film coated tablet. Engraved “CZ” over European bisect “2.5” on one side, “APO” on the other side. Each tablet typically weighs 82mg.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
5mg APO-CILAZAPRIL Reddish-brown, oval, biconvex, film coated tablet. Engraved “CZ” over European bisect “5” on one side, “APO” on the other side. Each tablet typically weighs 82mg.

The tablet can be divided into equal doses

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- APO-CILAZAPRIL is indicated in the treatment of all grades of essential hypertension and renovascular hypertension.
- APO-CILAZAPRIL 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**

**Standard dosage**

APO-CILAZAPRIL should be administered once daily. As food intake has no clinically significant influence on absorption, APO-CILAZAPRIL 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 2.5mg 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 APO-CILAZAPRIL is 2.5mg - 5mg once daily. If blood pressure is not adequately controlled with 5mg APO-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 APO-CILAZAPRIL should be initiated with a dose of 0.5mg or 0.25mg 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 APO-CILAZAPRIL 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.

**Congestive heart failure:**

APO-CILAZAPRIL can be used as adjunctive therapy with digitalis and/or diuretics in patients with congestive heart failure. Therapy with APO-CILAZAPRIL should be initiated at a recommended starting dose of 0.5mg once daily under close medical supervision. The dose should be increased to the lowest maintenance dose, 1mg daily, according to tolerability and clinical status. Further titration within the usual maintenance dose range of
1mg - 2.5mg daily should be carried out based on tolerability and the patient's response and clinical status. The usual maximum dose is 5mg 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 4.2 Dose and method of administration - 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 also 4.4 Special warnings and precautions for use, Hemodialysis/anaphylaxis). The following dosage schedules are recommended:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Initial dose of APO-CILAZAPRIL</th>
<th>Maximal dose of APO-CILAZAPRIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40 ml/min</td>
<td>1mg once daily</td>
<td>5mg once daily</td>
</tr>
<tr>
<td>10-40 ml/min</td>
<td>0.5mg once daily</td>
<td>2.5mg once daily</td>
</tr>
<tr>
<td>&lt;10 ml/min</td>
<td>0.25mg - 0.5mg once or twice a week according to blood pressure response</td>
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</tr>
</tbody>
</table>

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 0.5mg or less once daily, because significant hypotension may occur.

Elderly patients with hypertension:
Treatment with APO-CILAZAPRIL should be initiated with 0.5mg once daily. Thereafter, the maintenance dose of 1mg to 2.5mg must be adapted to individual tolerability, response and clinical status.

Elderly patients with congestive heart failure:
The recommended starting dose of APO-CILAZAPRIL 0.5mg 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.

Method of administration
Cilazapril is administered orally once daily and may be taken before or after a meal. The dose should always be taken at about the same time of day.

Maximum Tolerated Daily Dose
See above section on Dose.
4.3 Contraindications
• APO-CILAZAPRIL is contraindicated in patients who are hypersensitive to cilazapril, or to any of the excipients listed in section 6.1 or to other ACE inhibitors.
• Like other ACE inhibitors, APO-CILAZAPRIL is contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor.
• APO-CILAZAPRIL, like other ACE inhibitors, is contraindicated during pregnancy and lactation, (See Section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use
Like other ACE inhibitors, APO-CILAZAPRIL should be used with caution in patients with aortic stenosis or outflow obstruction.

The recommended starting dose of APO-CILAZAPRIL 0.5mg 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 immuno-suppressive 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, APO-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 4.2 Dose and method of administration – Patients with renal impairment.

Renal impairment:
Reduced dosages may be required for patients with renal impairment, depending on their creatinine clearance (see 4.2 Dose and method of administration – Patients with renal impairment). 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 APO-CILAZAPRIL is initiated, and serum potassium and renal function should be monitored carefully (see 5.1 Pharmacodynamic properties – Mechanism of Action and 4.5 Interaction with other medicines and other forms of interaction).

Dual blockade of the rennin-angiotensin-aldosterone system:
As a consequence of inhibiting the rennin-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 rennin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to the 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.

Surgery/anesthesia:
The use of ACE inhibitors in combination with anesthetic 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.

Hemodialysis/anaphylaxis:
Although the mechanism involved has not been definitely established, there is clinical evidence that hemodialysis or hemofiltration 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 desensitization 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 lactose 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 hypoglycemic agents or insulin.

4.5 Interaction with other medicines and other forms of interaction
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 APO-CILAZAPRIL is administered in combination with other blood pressure-lowering agents.

Potassium-sparing diuretics or potassium supplements administered together with APO-CILAZAPRIL can lead to increases in serum potassium; particularly in patients with renal impairment (see 4.4 Special warnings and precautions for use).

As with other ACE inhibitors, use of APO-CILAZAPRIL concomitantly with a non-steroidal anti-inflammatory (NSAID) may diminish the antihypertensive effect of APO-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 reported when cilazapril was administered concomitantly with nitrates, coumarin anticoagulants and H2-receptor blockers. No significant pharmacokinetic interactions between cilazapril and frusemide or thiazides were noted.

4.6 Fertility, pregnancy and lactation
Pregnancy
Category D

APO-CILAZAPRIL is contraindicated in pregnancy (see 4.3 Contraindications).

Foetotoxicity has been observed for ACE inhibitors in animals. Although there is no specific experience with APO-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 APO-CILAZAPRIL during pregnancy (see 4.3 Contraindications).
**APO-CILAZAPRIL**

**Breast-feeding**
It is not known whether cilazapril passes into human breast milk, but since animal data show the presence of cilazaprilat in rat milk, APO-CILAZAPRIL must not be administered to nursing mothers (see 4.3 Contraindications).

**Fertility**
There are no fertility data.

**4.7 Effects on 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 APO-CILAZAPRIL. However, it should be noted that dizziness may occasionally occur.

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

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

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.

**Hepatic 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.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
Immune system disorders:
As with other ACE inhibitors, angioneurotic edema 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 edema, APO-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 such as psoriasis dermatitis and psoriasis (exacerbation), 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 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use), but they have also occasionally been observed in patients with normal renal function, particularly in those receiving concomitant diuretics.

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 professional are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
While single doses of up to 160mg 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor,

ATC code: C09AA08

Mechanism of action

APO-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 APO-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 APO-CILAZAPRIL treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise. (See 4.4 Special warnings and precautions and 4.5 Interaction with other medicines and other forms of interaction).

APO-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 APO-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.

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

As with other ACE inhibitors, the blood pressure-lowering effect of APO-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.

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, APO-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 hemodynamic and clinical effects occur promptly and persist.
5.2 Pharmacokinetic properties

Cilazapril is efficiently absorbed and rapidly converted to the active form, cilazaprilat. Ingestion of food immediately prior to APO-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.

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

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 hemodialysis 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 have been 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 4.2 Dose and method of administration - Special dosage instructions – Congestive heart failure) should not be necessary.

5.3 Preclinical safety data

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-CILAZPRIL tablets contain the following excipients:

- Microcrystalline cellulose
- Starch (corn)
- Sodium stearyl fumarate
- Hydroxypropyl methylcellulose (hypromellose)
- Hydroxypropyl cellulose (hyprolose)
- Polyethylene glycol 8000 (macrogol 8000)
- Titanium dioxide
- Yellow ferric oxide (iron oxide yellow) [1mg tablets only]
- Red ferric oxide – orange shade # 34690 (iron oxide red – orange shade # 34690) [2.5mg and 5mg tablets only]
- Purified water
APO-CILAZAPRIL contains corn starch.

APO-CILAZAPRIL is gluten free and lactose free

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Shelf life: 2 years from the date of manufacture

6.4 Special precautions for storage
Store at or below 25°C
Protect from heat light and moisture.

6.5 Nature and contents of container
APO-CILAZAPRIL 1mg, 2.5mg and 5mg: HDPE bottles containing 200 tablets
Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627

Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL
APO-CILAZAPRIL 2.5mg & 5mg: 11 March 2010
APO-CILAZAPRIL 1mg: 20 July 2017
10. DATE OF REVISION OF THE TEXT
17 August 2017

SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole data sheet</td>
<td>Reformatted as per Medsafe new guideline for data sheet.</td>
</tr>
<tr>
<td>1</td>
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Congestive heart failure:
...The special dosage recommendation should thus be followed in congestive heart failure patients with impaired renal function (See 4.2 Dose and method of administration - 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 also Precautions 4.4 Special warnings and precautions for use, Hemodialysis/anaphylaxis). The following dosage schedules are recommended:

Method of administration
Cilazapril is administered orally once daily and may be taken before or after a meal. The dose should always be taken at about the same time of day.

Maximum Tolerated Daily Dose
See above section on Dose.

4.3 APO-CILAZAPRIL is contraindicated in patients who are hypersensitive to cilazapril, or to any of the excipients listed in section 6.1 components of the product or to other ACE inhibitors.

APO-CILAZAPRIL, like other ACE inhibitors, is contraindicated during pregnancy and lactation, (See 4.6 Fertility, pregnancy and lactation. Use in Pregnancy and lactation).

4.4 Symptomatic hypotension:
See Special dosage instructions 4.2 Dose and method of administration – 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 4.2 Dose and method of administration – Patients with renal impairment).

Serum potassium:
... Therefore, if concomitant use of such agents is indicated, their dosage should be reduced when APO-CILAZAPRIL is initiated, and serum potassium and renal function should be monitored carefully (see 5.1 Pharmacodynamic properties – Mechanism of Actions and 4.5 Interaction with other medicines and other forms of interaction).

4.5
Potassium-sparing diuretics or potassium supplements administered together with APO-CILAZAPRIL can lead to increases in serum potassium, particularly in patients with renal impairment (see Warnings and Precautions 4.4 Special warnings and precautions for use).

4.6
APO-CILAZAPRIL is contraindicated in pregnancy (see 4.3 Contraindications). Pregnant women should be informed of the potential hazards to the foetus and must not take APO-CILAZAPRIL during pregnancy (see 4.3 Contraindications).

Breast-feeding
It is not known whether cilazapril passes into human breast milk, but since animal data show the presence of cilazaprilat in rat milk, APO-CILAZAPRIL must not be administered to nursing mothers (see 4.3 Contraindications).

4.7
Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

4.8
Skin and subcutaneous tissue disorders:
Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photo-sensitivity, alopecia, and other hypersensitivity reactions such as psoriasis dermatitis and psoriasis (exacerbation), 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 4.4 Special warnings and precautions for use).

Laboratory test findings:
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 4.4 Special warnings and precautions for use), but they have also occasionally been observed in patients with normal renal function, particularly in those receiving concomitant diuretics.

4.9
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).
### 5.1 Pharmacotherapeutic group:
Angiotensin-converting enzyme (ACE) inhibitor, ATC code: C09AA08

**Actions**

In patients with normal renal function, serum potassium usually remains within the normal range during APO-CILAZAPRIL treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise. (See 4.4 Special warnings and precautions, and 4.5 Interaction with other medicines and other forms of interactions).

### 5.2 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 4.2 Dose and method of administration - Special dosage instructions – Congestive heart failure) should not be necessary.

### 6.5 APO-CILAZAPRIL 1mg, 2.5mg & 5mg: HDPE Bottles containing 200 tablets

### 6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

### 7 Prescription only medicine

### 8 Apotex NZ Ltd.
32 Hillside Road
Glenfield
Private Bag 102995
North Shore Mail Centre
AUCKLAND 0627
Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

### 9 9. Date of First Approval

- APO-CILAZAPRIL 2.5mg & 5mg: 11 March 2010
- APO-CILAZAPRIL 1mg: 20 July 2017

### 10 10. Date of Preparation Revision of the Text

- 20 June 2016 - 17 August 2017