ACE inhibitors

See also Heart failure p 233, Acute coronary syndromes p 312, Hypertension p 246
For drug interactions see ACE inhibitors p 877

Also known as angiotensin converting enzyme inhibitors.
Captopril p 255
Enalapril p 256
Fosinopril p 256
Lisinopril p 256
Perindopril p 257
Quinapril p 257
Ramipril p 258
Trandolapril p 258

Mode of action
ACE inhibitors block conversion of angiotensin I to angiotensin II and also inhibit the breakdown of bradykinin. They reduce the effects of angiotensin II-induced vasoconstriction, sodium retention and aldosterone release. They also reduce the effect of angiotensin II on sympathetic nervous activity and growth factors.

Indications
Hypertension
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)
Diabetic nephropathy
Prevention of progressive renal failure in patients with persistent proteinuria (>1 g daily)
Post MI

Precautions
Angioedema (hereditary, idiopathic or ACE inhibitor-induced)—ACE inhibitors increase risk of further episodes; use alternative class or seek specialist advice.
Volume or sodium depletion—may activate the renin–angiotensin system; this may result in excessive hypotension when an angiotensin-blocking drug is started; correct (eg by reducing diuretic dosage) before treatment and/or monitor carefully.
Primary hyperaldosteronism—an ACE inhibitor may be ineffective; seek specialist advice.
Black African or Caribbean descent—antihypertensive effect of ACE inhibitor monotherapy may be reduced (generally a calcium channel blocker or thiazide diuretic is more effective).

Adverse effects
Common (>1%)
- hypotension, headache, dizziness, cough (below), hyperkalaemia, fatigue, nausea, renal impairment

Renal
Renal impairment increases risk of hyperkalaemia and may affect the excretion of some ACE inhibitors; use lower initial doses and monitor potassium concentration.
Renal impairment may worsen, especially in people with hypovolaemia, or if used with NSAIDs (including selective COX-2 inhibitors).
Serum creatinine may increase after starting treatment or increasing the dose (usually stabilises within the first 2 months):
  - if increase is <30% or glomerular filtration rate (GFR) reduction is <25%, there is no need to adjust dose
  - if increase is >30% (or GFR reduction is >25%), investigate other causes and if necessary, reduce dose or stop ACE inhibitor and consider specialist referral.

ACE inhibitors increase risk of renal failure in bilateral renal artery stenosis.
Haemodialysis with high flux polyacrylonitrile membranes (AN 69) may result in anaphylactoid reactions; similar reactions may occur in patients on low density lipoprotein apheresis with dextran sulfate.

Surgery
Excessive hypotension may occur during anaesthesia and after surgery.

Elderly
May be more predisposed to first-dose hypotension, hyperkalaemia and renovascular disease than younger patients. Start treatment with lower doses; monitor renal function closely.

Women
Avoid in women planning to conceive or who are using inadequate contraception.

Pregnancy
Avoid use; change women to an alternative antihypertensive as soon as possible during the first trimester. Use in the second and third trimesters may cause fetal renal dysfunction and oligohydramnios, and subsequently fetal death.
Contraindicated by manufacturers; Australian category D.

Breastfeeding
No adverse effects in infants reported with captopril or enalapril; insufficient information to confirm safety of other ACE inhibitors.

Adverse effects
Common (>1%)
- hypotension, headache, dizziness, cough (below), hyperkalaemia, fatigue, nausea, renal impairment

Infrequent (0.1–1%)
angioedema (below), rash (especially captopril), diarrhoea, elevated hepatic aminotransferases and bilirubin

Rare (<0.1%)
hepatitis (cholestatic or hepatocellular), pancreatitis, hyponatraemia, photosensitivity, psoriasis
Cough
A persistent, nonproductive cough is common; it is not dose-dependent and is unlikely to respond to treatment. It can occur within days to months of starting treatment. The cough may be mild and tolerable, however, some patients need to stop treatment (usually improves within 1–4 weeks of stopping).

Angioedema
May affect the face, lips, tongue, upper airway, and less often, the GI tract (causing abdominal pain, vomiting and diarrhoea). It can occur within the first week of treatment, but is possible months or years later.

Comparative information
Advantages for specific ACE inhibitors are claimed based on pharmacokinetic, metabolic or tissue ACE-binding characteristics, however, these do not translate into significant clinical differences. Most (except captopril) maintain an antihypertensive effect for up to 24 hours and can be given once daily. Most are available as fixed-dose combinations (p 248) with a diuretic (hydrochlorothiazide or indapamide) or a calcium channel blocker.

Dosage in heart failure
Begin with a low dose (risk of hypotension, particularly if the patient is elderly or taking a diuretic), then gradually titrate upwards at short intervals (eg every 2–4 weeks) to the highest tolerable maintenance dose. A more rapid dose escalation may be possible in closely monitored situations.

Counselling
You may feel dizzy when you start taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy or light-headed. Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

Practice points
• when starting an ACE inhibitor:
  – stop potassium supplements and potassium-sparing diuretics
  – in heart failure, consider reducing dose or withholding other diuretics for 24 hours before starting an ACE inhibitor
  – review use of NSAIDs (including selective COX-2 inhibitors)
  – start with a low dose
• check renal function and electrolytes before starting an ACE inhibitor and review after 1–2 weeks

Treatment with an ACE inhibitor and a sartan
• in trials the combination worsened renal function and increased the risk of symptomatic hypotension and hyperkalaemia
• the combination did not provide additional benefit in patients at high risk of vascular disease nor improve survival in patients with left ventricular failure/dysfunction after MI
• aldosterone antagonists are preferred to sartans in patients with heart failure who remain symptomatic despite optimal treatment with an ACE inhibitor and a beta-blocker

• despite conflicting trial results, it may be an option, eg for selected patients with chronic heart failure or non-responsive BP, seek specialist advice

Captopril
For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)
Post MI in patients with left ventricular dysfunction
Diabetic nephropathy (type 1 diabetes)

Precautions
Collagen vascular disorders (eg scleroderma, systemic lupus erythematosus), severe renal impairment—may predispose to neutropenia or agranulocytosis.

Adverse effects
Infrequent (0.1–1%)
taste disturbances
Rare (<0.1%)
pemphigus

Dosage
Adult

Hypertension
Initially 12.5 mg twice daily, increased at intervals of 2–4 weeks to 25–50 mg twice daily.

Heart failure
See also Dosage in heart failure p 255
Initially 6.25 mg 3 times daily, increased at 2-week intervals to 25–75 mg twice daily. Maximum 150 mg daily.

Post MI
Initiate treatment in stable patients 3 days post MI at 6.25 mg 3 times daily; increase up to 25 mg 3 times daily over several days to final target dose of 50 mg 3 times daily.

Diabetic nephropathy
25 mg 3 times daily.

Renal impairment, elderly or taking a diuretic
Initially 6.25 mg twice daily.

Child
1 month – 12 years, 0.1–0.3 mg/kg 2 or 3 times daily, increasing if needed to a maximum of 6 mg/kg daily (4 mg/kg daily if <1 year). Give the first dose under medical supervision.

Administration advice
Oral liquid: mix with a drink such as water, fruit juice, tea, coffee or cola, and take immediately.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
<th>Code</th>
<th>PBS Code</th>
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<tr>
<td>12.5 mg (scored)</td>
<td>90, Zedace®</td>
<td>PBS</td>
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<tr>
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<td>50 mg</td>
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<td>90, Capoten®</td>
<td>PBS</td>
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<td>Oral liquid, 5 mg/mL, 95 mL</td>
<td>Capoten, PBS-R†</td>
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</table>

† if unable to take an ACE inhibitor as a tablet/capsule
a other generic brands available
Enalapril

For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension (includes fixed-dose combination with hydrochlorothiazide or lercanidipine)
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)
Asymptomatic left ventricular dysfunction

Dosage

**Hypertension**
**Adult**

Child >50 kg, initially 5 mg daily, increased at intervals of 1–2 weeks up to 10–40 mg daily in 1 or 2 doses.

Child <50 kg, 0.1 mg/kg (maximum 2.5 mg) daily in 1 or 2 doses, increasing gradually if necessary over 2 weeks to maximum 0.6 mg/kg (not to exceed 20 mg) daily in 1 or 2 doses. Give the first dose under medical supervision.

**Fixed-dose combination with hydrochlorothiazide or lercanidipine**
For additional information see Hydrochlorothiazide p 252, Lercanidipine p 265

**Adult**, 1 tablet once daily (of any strength).

**Heart failure**
See also Dosage in heart failure p 255

**Adult**, initially 2.5 mg daily, increased gradually up to 10–20 mg daily given in 1 or 2 doses.

**Left ventricular dysfunction**
**Adult**, initially 2.5 mg daily, increased gradually up to 10 mg twice daily.

**Renal impairment, elderly or taking a diuretic**
**Adult**, initially 2.5 mg once daily.

| Tab, 5 mg, 30, Enalapril a, PBS |
| Tab, 5 mg (scored), 30, Acetec, Auspril, Malean a, PBS |
| Tab, 5 mg (scored), 30, Renitec M |
| Tab, 10 mg, 30, Enalapril a, PBS |
| Tab, 10 mg (scored), 30, Acetec, Auspril, Malean, Renitec a, PBS |
| Tab, 20 mg, 30, Renitec a, PBS |
| Tab, 20 mg (scored), 30, Acetec, Malean, Auspril a, PBS |

**Fixed-dose combinations**
| Tab, enalapril 20 mg, hydrochlorothiazide 6 mg, 30, Renitec Plus 20/6, PBS-R |
| Tab, enalapril 20 mg, hydrochlorothiazide 6 mg (scored), 30, Enalapril/HCT 20/6 a, PBS-R |
| Tab, enalapril 10 mg, lercanidipine 10 mg, 28, Zan-Extra 10/10, PBS-R |
| Tab, enalapril 20 mg, lercanidipine 10 mg, 28, Zan-Extra 10/20, PBS-R |

**Heart failure**
See also Dosage in heart failure p 255

**Adult**, initially 10 mg once daily, increased up to 40 mg once daily.

**Fixed-dose combination with hydrochlorothiazide**
For additional information see Hydrochlorothiazide p 252

**Adult**, 1 tablet once daily (of either strength).

**Renal impairment, elderly or taking a diuretic**
**Adult**, initially 5–10 mg once daily.

| Tab, 10 mg, 30, Monopril a, PBS |
| Tab, 10 mg (scored), 30, Fosinopril, Monace, PBS |
| Tab, 20 mg, 30, Fosinopril a, PBS |
| Tab, 20 mg (scored), 30, Monace, Monopril, PBS |

**Fixed-dose combinations**
| Tab, fosinopril 10 mg, hydrochlorothiazide 12.5 mg, 30, Monopril 10/12.5 a, PBS-R |
| Tab, fosinopril 20 mg, hydrochlorothiazide 12.5 mg, 30, Fosetic 20/12.5, Monopril 20/12.5 a, PBS-R |

a hypertension (not for starting treatment), see PBS
a other generic brands available

Lisinopril

For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)
Post MI, acute treatment

Dosage

**Hypertension**
**Adult**

Initially 5–10 mg once daily; if necessary, increase at intervals of 2–4 weeks up to 20 mg once daily. Maximum 40 mg daily.

Child >6 years, 0.07 mg/kg (maximum 5 mg) once daily; if necessary, increase up to 40 mg once daily. Give first dose under medical supervision.

**Heart failure**
See also Dosage in heart failure p 255

**Adult**, initially 2.5 mg once daily, increased at 4-week intervals up to 20–40 mg once daily according to clinical response.

**Post MI**
**Adult**, initially 5 mg within 24 hours of the onset of symptoms (2.5 mg in patients with systolic BP <120 mm Hg), followed by 5 mg after 24 hours; then 10 mg once daily for 6 weeks; continue treatment in patients developing heart failure.

**Renal impairment, elderly or taking a diuretic**
**Adult**, initially 2.5–5 mg once daily.

| Tab, 5 mg, 30, Lisinopril a, PBS |
| Tab, 5 mg (scored), 30, Fosipril, Zestril, Zinopril a, PBS |
| Tab, 10 mg, 30, Zestril, Zinopril a, PBS |
| Tab, 10 mg (scored), 30, Fosipril, Prinivil a, PBS |
| Tab, 20 mg, 30, Zestril, Zinopril a, PBS |
| Tab, 20 mg (scored), 30, Fosipril, Prinivil a, PBS |

a other generic brands available
Perindopril

For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension (includes fixed-dose combination with indapamide)
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)
Reduction of risk of MI or cardiac arrest in people with established coronary heart disease without heart failure

Fixed-dose combination with amlodipine
Hypertension if already maintained on perindopril and amlodipine
Stable coronary heart disease if already maintained on perindopril and amlodipine

Dosage

Dose equivalence
2.5 mg of perindopril arginine is equivalent to 2 mg of perindopril erbumine.

Hypertension

Perindopril arginine, adult, initially 2.5 mg once daily.
Maximum 10 mg once daily.

Perindopril erbumine, adult, initially 4 mg once daily.
Maximum 8 mg once daily.

Elderly or at risk of ACE inhibitor-induced hypotension

Perindopril arginine, adult, initially 2.5 mg once daily.
Perindopril erbumine, adult, initially 2 mg once daily.

Fixed-dose combination of perindopril arginine or erbumine with indapamide

For additional information see Indapamide p 252
Adul, 1 tablet once daily (of any strength).

Heart failure

See also Dosage in heart failure p 255
Perindopril arginine, adult, initially 2.5 mg once daily; increase up to 5 mg once daily.
Perindopril erbumine, adult, initially 2 mg once daily; increase up to 4 mg once daily.

Reduction of risk of cardiovascular events

Perindopril arginine, adult, initially 5 mg once daily for 2 weeks; increase up to 10 mg once daily depending on tolerance and renal function.
Perindopril erbumine, adult, initially 4 mg once daily for 2 weeks; increase up to 8 mg once daily depending on tolerance and renal function.

Elderly

Perindopril arginine, initially 2.5 mg once daily for 1 week, then 5 mg once daily the next week; increase up to 10 mg once daily depending on tolerance and renal function.
Perindopril erbumine, initially 2 mg once daily for 1 week, then 4 mg once daily the next week; increase up to 8 mg once daily depending on tolerance and renal function.

Renal impairment

Adult, initial dose for perindopril arginine is 2.5 mg, perindopril erbumine 2 mg, then give this dose according to CrCl:
- 30–60 mL/minute, once daily.
- 15–30 mL/minute, on alternate days.
- <15 mL/minute, on day of dialysis.

Revision of dose in renal impairment

Adult, reduce by half if CrCl 15–30 mL/minute, follow up in 1 month.

Perindopril arginine

Maximum 8 mg once daily.

Perindopril erbumine

Maximum 10 mg once daily.

For drug interactions see ACE inhibitors p 877

Practice points

- health professionals should be aware of the possibility of errors due to confusion between perindopril arginine and perindopril erbumine

Fixed-dose combination of perindopril arginine with amlodipine

For additional information see Amlodipine p 264
If changing from perindopril erbumine, use the dose equivalence above to establish the correct strength of perindopril arginine.

Adult, 1 tablet once daily (of any strength).

Perindopril arginine

tab, 2.5 mg, 30, Coversyl, Prexum, PBS
tab, 5 mg (scored), 30, Coversyl, Prexum, PBS
tab, 10 mg, 30, Coversyl, Prexum, PBS

Fixed-dose combinations

tab, perindopril arginine 5 mg, amlodipine 5 mg, 30, Coveram 5/5, Reaptan 5/5, PBS-R1,2

Perindopril erbumine

tab, 2.5 mg, 30, Coversyl, Prexum, PBS

Fixed-dose combinations

tab, perindopril arginine 5 mg, amlodipine 10 mg, 30, Coveram 5/10, Reaptan 5/10, PBS-R1,2

tab, perindopril arginine 10 mg, amlodipine 5 mg, 30, Coveram 10/5, Reaptan 10/5, PBS-R1,2

Quinapril

For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension (includes fixed-dose combination with hydrochlorothiazide)
Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)

Dosage

Hypertension

Adult, initially 5–10 mg once daily; increase at 4-week intervals to 10–40 mg daily in 1 or 2 doses.

Fixed-dose combination with hydrochlorothiazide

For additional information see Hydrochlorothiazide p 252

Adult, 1 tablet once daily (of either strength).

Heart failure

See also Dosage in heart failure p 255

Adult, initially 5 mg daily; increase at weekly intervals to 5–10 mg twice daily. If 10 mg twice daily is tolerated, change to 20 mg once daily after 1 month.

Renal impairment, elderly or taking a diuretic

Adult, initially 2.5–5 mg once daily.
Ramipril
For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension (includes fixed-dose combination with felodipine)
Post MI in patients with heart failure
Prevention of MI, stroke, cardiovascular death or need for revascularisation procedures in patients >55 years with:
- coronary artery disease, stroke or peripheral vascular disease,
or
- diabetes and 1 or more risk factors (hypertension, smoking, microalbuminuria, high total cholesterol, low HDL cholesterol, previous vascular disease)
Prevention of progressive renal failure in patients with persistent proteinuria (>1 g daily)

Dosage
Hypertension
Adult, 2.5 mg once daily, increase after 2–3 weeks to 5 mg if necessary. Maximum 10 mg daily in 1 or 2 doses.

Fixed-dose combination with felodipine
For additional information see Felodipine p 265
Adult, 1 tablet once daily (of either strength).

Heart failure
Adult, initially 2.5 mg twice daily, beginning 2–10 days after MI in patients who are haemodynamically stable; increase at intervals of 1–3 days to 5–10 mg daily in 2 divided doses.

Increased cardiovascular risk
Adult, initially 2.5 mg once daily, increase after 1 week to 5 mg once daily and after 3 weeks to 10 mg once daily.

Renal impairment, elderly or taking a diuretic
Adult, initially 1.25 mg once daily.

Proteinuria
Adult, initially 1.25 mg once daily, double at intervals of 2–3 weeks, depending on tolerance, up to 5 mg once daily.

Trandolapril
For additional information see ACE inhibitors p 254
For drug interactions see ACE inhibitors p 877

Indications
Hypertension, including fixed-dose combination with verapamil (p 267)
Post MI in patients with left ventricular dysfunction

Precautions
Hepatic
Use a lower starting dose in those with hepatic impairment.

Dosage
Hypertension
Adult, 1 mg once daily; if necessary, increase after 2–4 weeks to 2 mg once daily. Maximum 4 mg once daily.

Post MI
Adult, initiate treatment in stable patients 3 days post MI. Use initial 0.5 mg test dose followed by 1 mg once daily for 3 days. Increase to 2 mg once daily for 4 weeks then to a maximum dose of 4 mg once daily if tolerated.

Renal or hepatic impairment, elderly or taking a diuretic
Adult, initially 0.5 mg once daily.

Other products containing trandolapril are listed in Verapamil p 267.

cap, 0.5 mg, 28, Dolapril, Gopten, Tranalpha®, PBS
cap, 1 mg, 28, Dolapril, Gopten, Tranalpha®, PBS
cap, 2 mg, 28, Dolapril, Gopten, Tranalpha®, PBS
cap, 4 mg, 28, Dolapril, Gopten, Tranalpha®, PBS

Other generic brands available