

6.3.3 ACE inhibitors

See also *Heart failure p 237, Acute coronary syndromes p 320, Hypertension p 252*
For drug interactions see *ACE inhibitors p 929*

Also known as angiotensin converting enzyme inhibitors.

Captopril p 262

Enalapril p 262

Fosinopril p 262

Lisinopril p 263

Perindopril p 263

Quinapril p 264

Ramipril p 264

Trandolapril p 265

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

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).

Treatment with drugs that can increase potassium concentration, eg trimethoprim, ciclosporin—increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.

Cardiovascular

Limited data suggest that ACE inhibitors are beneficial in selected patients with aortic stenosis (theoretically they may cause coronary hypoperfusion, systemic hypotension and reduced renal function); caution is needed to avoid hypotension. Patients with peripheral vascular disease or atherosclerosis may be more likely to have renal artery stenosis, increasing the risk of renal failure.

Angioedema

Treatment with sacubitril with valsartan is contraindicated with an ACE inhibitor due to the increased risk of angioedema (allow 36 hours between stopping an ACE inhibitor and starting sacubitril with valsartan).

ACE inhibitors increase the risk of further episodes of angioedema in people with hereditary, idiopathic or ACE inhibitor-induced angioedema; use alternative class or seek specialist advice.

Treatment with an mTOR inhibitor (eg everolimus), a dipeptidyl peptidase-4 inhibitor (eg sitagliptin), or alteplase may also increase the risk of angioedema.

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.

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

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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 254) 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

See also Table 6–1 Management of systolic heart failure p 237

- 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
- 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 260

For drug interactions see ACE inhibitors p 929

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

Oral, 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 261

Oral, initially 6.25 mg 3 times daily, increased at 2-week intervals to 25–75 mg twice daily.

Maximum 150 mg daily.

Post MI

Start 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

Oral, 25 mg 3 times daily.

Renal impairment, elderly or taking a diuretic

Initially 6.25 mg twice daily.

Child 1 month – 12 years

Oral, 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.

tab, 12.5 mg (scored), 90, Zedace^a, PBS
tab, 25 mg (scored), 90, Capoten, Zedace^a, PBS
tab, 50 mg (scored), 90, Capoten, Zedace^a, PBS
oral liquid, 5 mg/mL, 95 mL, Capoten, PBS-R¹

¹ if unable to take an ACE inhibitor as a tablet/capsule

^a other generic brands available

Enalapril

For additional information see ACE inhibitors p 260
For drug interactions see ACE inhibitors p 929

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

Oral, 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

Oral, 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 258, Lercanidipine p 272
Adult, 1 tablet once daily (of any strength).

Heart failure

See also Dosage in heart failure p 261

Adult, oral, initially 2.5 mg daily, increased gradually up to usual maintenance dose of 10–20 mg daily given in 1 or 2 doses.

Left ventricular dysfunction

Adult, oral, 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[®], PBS
tab, 5 mg (scored), 30, Acetec, Malean[®], PBS
tab, 5 mg (scored), 30, Renitec[®] M
tab, 10 mg, 30, Enalapril[®], PBS
tab, 10 mg (scored), 30, Acetec, Malean, Renitec[®], PBS
tab, 20 mg, 30, Renitec[®], PBS
tab, 20 mg (scored), 30, Acetec, Malean[®], PBS

Fixed-dose combinations

tab, enalapril 20 mg, hydrochlorothiazide 6 mg, 30, Renitec Plus 20/6, PBS-R¹
tab, enalapril 20 mg, hydrochlorothiazide 6 mg (scored), 30, Enalapril/HCT 20/6[®], PBS-R¹
tab, enalapril 10 mg, lercanidipine 10 mg, 28, Zan-Extra 10/10, PBS-R¹
tab, enalapril 20 mg, lercanidipine 10 mg, 28, Zan-Extra 10/20, PBS-R¹

¹ hypertension (not for starting treatment), see PBS
^a other generic brands available

Fosinopril

For additional information see ACE inhibitors p 260
For drug interactions see ACE inhibitors p 929

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, oral, initially 10 mg once daily, increased up to 40 mg once daily.

Fixed-dose combination with hydrochlorothiazide

For additional information see Hydrochlorothiazide p 258

1 tablet once daily.

Heart failure

See also Dosage in heart failure p 261

Adult, oral, initially 5–10 mg once daily, increased up to 10–40 mg once daily.

Renal impairment, elderly or taking a diuretic

Initially 5–10 mg once daily.

tab, 10 mg, 30, Fosinopril[®], PBS
tab, 10 mg, 30, Monopril
tab, 10 mg (scored), 30, Fosipril, Monace, PBS^a
tab, 20 mg, 30, Fosipril[®], PBS
tab, 20 mg (scored), 30, Monace, PBS

Fixed-dose combinations

tab, fosinopril 20 mg, hydrochlorothiazide 12.5 mg, 30, Fosetic 20/12.5[®], PBS-R

¹ hypertension (not for starting treatment), see PBS
^a other generic brands available

Lisinopril

For additional information see ACE inhibitors p 260
For drug interactions see ACE inhibitors p 929

Indications

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

Dosage

Hypertension

Adult, oral, 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, oral 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 261

Adult, oral, 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, oral, 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 (scored), 30, Fibsol, Zestril, Zinopril[®], PBS
tab, 10 mg, 30, Zestril, Zinopril[®], PBS
tab, 10 mg (scored), 30, Fibsol[®], PBS
tab, 20 mg, 30, Zestril, Zinopril[®], PBS
tab, 20 mg (scored), 30, Fibsol[®], PBS

^a other generic brands available

Perindopril

For additional information see ACE inhibitors p 260

For drug interactions see ACE inhibitors p 929

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

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Dosage

Dose equivalence

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

Hypertension

Perindopril arginine, adult, oral, start at 5 mg once daily. Maximum 10 mg once daily.

Perindopril erbumine, adult, oral, start at 4 mg once daily. Maximum 8 mg once daily.

Elderly or at risk of ACE inhibitor-induced hypotension

Perindopril arginine, start at 2.5 mg once daily.

Perindopril erbumine, start at 2 mg once daily.

Fixed-dose combination of perindopril arginine or erbumine with indapamide

For additional information see *Indapamide* p 259
1 tablet once daily (of any strength).

Heart failure

See also *Dosage in heart failure* p 261

Perindopril arginine, adult, oral, start at 2.5 mg once daily; increase up to 5 mg once daily.

Perindopril erbumine, adult, oral, start at 2 mg once daily; increase up to 4 mg once daily.

Reduction of risk of cardiovascular events

Perindopril arginine, adult, oral, start at 5 mg once daily for 2 weeks; increase up to 10 mg once daily depending on tolerance and renal function.

Perindopril erbumine, adult, oral, start at 4 mg once daily for 2 weeks; increase up to 8 mg once daily depending on tolerance and renal function.

Elderly

Perindopril arginine, start at 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, start at 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

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.

Fixed-dose combination of perindopril arginine with amlodipine

For additional information see *Amlodipine* p 270

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).

Practice points

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

Perindopril arginine

tab, 2.5 mg, 30, *Coversyl*, *Prexum*^a, PBS

tab, 5 mg (scored), 30, *Coversyl*, *Prexum*^a, PBS

tab, 10 mg, 30, *Coversyl*, *Prexum*^a, PBS

Fixed-dose combinations

tab, perindopril arginine 5 mg, amlodipine 5 mg, 30, *Coveram 5/5*, *Reaptan 5/5*^a, PBS-R^{1,2}

tab, perindopril arginine 5 mg, amlodipine 10 mg, 30, *Coveram 5/10*, *Reaptan 5/10*^a, PBS-R^{1,2}

tab, perindopril arginine 10 mg, amlodipine 5 mg, 30, *Coveram 10/5*, *Reaptan 10/5*^a, PBS-R^{1,2}

tab, perindopril arginine 10 mg, amlodipine 10 mg, 30, *Coveram 10/10*, *Reaptan 10/10*^a, PBS-R^{1,2}

tab, perindopril arginine 2.5 mg, indapamide 0.625 mg (scored), 30, *Coversyl Plus LD 2.5/0.625*, *Prexum Combi LD 2.5/0.625*, PBS

tab, perindopril arginine 5 mg, indapamide 1.25 mg, 30, *Coversyl Plus 5/1.25*, *Prexum Combi 5/1.25*, PBS-R¹

tab, perindopril arginine 5 mg, indapamide 1.25 mg, 30, *Coversyl Plus 5/1.25*, *Prexum Combi 5/1.25*, PBS-R¹

Perindopril erbumine

tab, 2 mg, 30, *Idaprex*, *Indosyl Mono*, *Perindo*^a, PBS

tab, 4 mg (scored), 30, *Idaprex*, *Indosyl Mono*, *Perindo*^a, PBS

tab, 8 mg, 30, *Idaprex*, *Indosyl Mono*, *Perindo*^a, PBS

tab, 8 mg (scored), 30, *Perindopril*^a, PBS

Fixed-dose combinations

tab, perindopril erbumine 4 mg, indapamide 1.25 mg, 30, *Idaprex Combi 4/1.25*, *Indosyl Combi 4/1.25*, *Perindo Combi 4/1.25*^a, PBS-R¹

¹ hypertension; not for initiation of treatment, see PBS

² stable coronary heart disease when stabilised on both drugs

^a other generic brands available

Quinapril

For additional information see ACE inhibitors p 260

For drug interactions see ACE inhibitors p 929,

Quinapril p 929

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, oral, 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 258

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

Heart failure

See also *Dosage in heart failure* p 261

Adult, oral, 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

Initially 2.5–5 mg once daily.

tab, 5 mg (scored), 30, *Accupril, Acquin, Qpril*, PBS
 tab, 10 mg (scored), 30, *Accupril, Acquin, Qpril*^a, PBS
 tab, 20 mg (scored), 30, *Accupril, Acquin, Qpril*^a, PBS

Fixed-dose combinations

tab, quinapril 10 mg, hydrochlorothiazide 12.5 mg (scored), 30, *Accuretic 10/12.5*, PBS-R¹
 tab, quinapril 20 mg, hydrochlorothiazide 12.5 mg (scored), 30, *Accuretic 20/12.5*, PBS-R¹

¹ hypertension (not for starting treatment), see PBS

^a other generic brands available

Ramipril

For additional information see ACE inhibitors p 260
 For drug interactions see ACE inhibitors p 929

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, oral 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 272

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

Heart failure

Adult, oral, 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 up to 10 mg daily in 2 doses.

Increased cardiovascular risk

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

Proteinuria

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

Renal impairment, elderly or taking a diuretic

Initially 1.25 mg once daily.

tab, 1.25 mg, 30, *Tryzan*^a, PBS
 tab, 1.25 mg (scored), 30, *Ramace, Tritace, Vasalace*^a, PBS
 tab, 2.5 mg (scored), 30, *Ramace, Tritace, Tryzan, Vasalace*^a, PBS
 tab, 5 mg (scored), 30, *Ramace, Tritace, Tryzan, Vasalace*^a, PBS
 tab, 10 mg (scored), 30, *Tritace, Tryzan, Vasalace*^a, PBS
 cap, 1.25 mg, 30, *Tryzan, Vasalace*^a, PBS
 cap, 2.5 mg, 30, *Tryzan, Vasalace*^a, PBS
 cap, 5 mg, 30, *Tryzan, Vasalace*^a, PBS
 cap, 10 mg, 30, *Ramace, Tritace, Tryzan, Vasalace*^a, PBS

Fixed-dose combinations

tab, ramipril 2.5 mg, felodipine (controlled release) 2.5 mg, 30, *Triasyn 2.5/2.5*, PBS-R¹
 tab, ramipril 5 mg, felodipine (controlled release) 5 mg, 30, *Triasyn 5/5*, PBS-R¹

¹ hypertension (not for starting treatment), see PBS

^a other generic brands available

Trandolapril

For additional information see ACE inhibitors p 260

For drug interactions see ACE inhibitors p 929

Indications

Hypertension, including fixed-dose combination with verapamil (p 274)

Post MI in patients with left ventricular dysfunction

Precautions

Hepatic

Use a lower starting dose in those with hepatic impairment.

Dosage

Adult

Hypertension

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

Post MI

Oral, start 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

Initially 0.5 mg once daily.

Other products containing trandolapril are listed in Verapamil p 274.

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