Formulary decision guide: Ramipril 2.5 mg/5 ml oral solution

Guidelines in practice

Product current status:		
Product proposed status:		
Date of next meeting:		
Decision:	**Yes**	**No**
Restricted use:		

Drug name

Ramipril 2.5 mg/5 ml oral solution

Indications

Ramipril oral solution is indicated for patients unable/unwilling to swallow ramipril tablets or capsules, for:[1]

- treatment of hypertension
- cardiovascular prevention:
  - reduction of cardiovascular morbidity and mortality in patients with manifest atherothrombotic CVD (history of CHD or stroke or peripheral vascular disease) or diabetes with at least one cardiovascular risk factor
- treatment of renal disease (please refer to the summary of product characteristics[1] available at **www.medicines.org.uk/emc**)
- treatment of symptomatic heart failure
- secondary prevention after acute MI—reduction of mortality from the acute phase of MI in patients with clinical signs of heart failure when started >48 h following acute MI.

Dosage

- Ramipril oral solution should be taken at the same time each day[1]
- It can be taken before, with, or after meals[1]
- Please refer to the summary of product characteristics[1] available at **www.medicines.org.uk/emc** for use in specific patients.

Mode of action

- ACE inhibitors, such as ramipril, lower blood pressure by reducing angiotensin II levels in the body
- Angiotensin II in the bloodstream causes blood vessels to constrict and become narrower. It also triggers a hormonal response that increases the amount of fluid retained by the body.

NICE recommendations

- An ACE inhibitor (or a low-cost ARB) is recommended as the first-line treatment option for hypertension in patients under the age of 55 years—**NB** patients >55 years and those of African or Caribbean family origin should be given a CCB as the first-line treatment[2]
- All patients should be offered an ACE inhibitor post-MI as early as possible, and have doses titrated up every 1–2 weeks[3]
- Patients should continue treatment with an ACE inhibitor regardless of LV function[3]
- All patients with CHF due to LV systolic dysfunction should be offered an ACE inhibitor (or ARB) and a beta blocker[4]
- Commissioners should ensure that they implement this guidance and review patients after each dose increase.[4]

Quality and outcomes framework

- Achievement of the QOF indicators on management of heart failure requires:
  - percentage of patients with heart failure due to LV dysfunction on an ACE inhibitor or ARB (HF3)[5]
  - percentage of patients with heart failure due to LV dysfunction on a combination of an ACE inhibitor or ARB and beta blocker (HF4).[5]

Evidence for use

- Ramipril is one of the 20 most prescribed drugs in the UK[6]
- Almost 60% of patients aged >60 years experience some difficulty in swallowing solid-dose medications[7]
- Circulatory diseases (heart disease and stroke) are the leading cause of death in England and Wales.[8]

Compliance and cost effectiveness

- ACE inhibitors are the most cost-effective option in the treatment of CVD episodes[9]
- Swallowing difficulties might be one factor that adversely affects compliance, particularly in the elderly and stroke patients.

Contraindications

- Hypersensitivity to ramipril, to any of the excipients or any other ACE inhibitors[1]
- History of angioedema[1]
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces[1]
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney[1]
- Second and third trimester of pregnancy[1]
- Do not use in patients with hypotensive or haemodynamically unstable states.[1]

Precautions and side-effects

- Please refer to the summary of product characteristics[1] available at **www.medicines.org.uk/emc/**

CVD=cardiovascular disease; CHD=coronary heart disease; MI=myocardial infarction; ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blocker; CCB=calcium-channel blocker; CHF=chronic heart failure; LV=left ventricular; QOF=quality and outcomes framework

This formulary decision guide was developed from content provided by Rosemont Pharmaceuticals Ltd in a format developed by *Guidelines in Practice*. It has been reviewed by a member of the *Guidelines in Practice* editorial board. At all times editorial control has remained with *Guidelines in Practice*

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Key points

- The following patients, who may become non-adherent, benefit from ramipril oral solution:
  - those aged >60 years who might have difficulty swallowing ramipril tablets or other solid-dose medications[7]
  - those with transient swallowing difficulties, e.g. patients who have suffered a stroke.

References

1. Rosemont Pharmaceuticals Ltd. *Ramipril 2.5 mg/5 ml oral solution. Summary of product Characteristics*. 2011.
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4. National Institute for Health and Clinical Excellence. *Quality standard for chronic heart failure*. London: NICE, 2011. Available at: www.nice.org.uk/media/D6F/93/CHFQualityStandard.pdf
5. British Medical Association. NHS Employers. *Quality and outcomes framework guidance for GMS contract 2012/13*. London: BMA, NHS Employers, 2012. Available at: www.bma.org.uk/employmentandcontracts/independent_contractors/quality_outcomes_framework/qofchanges2012.jsp#.T3WeP5jrGCF
6. NHS Information Centre. *Prescription cost analysis: England 2010*. London: Health and Social Care Information Centre, Prescribing Support Unit, 2011. Available at: www.ic.nhs.uk/webfiles/publications/007_Primary_Care/Prescribing/Prescription_Cost_Analysis_England_2010/Prescription_Cost_Analysis_2010.pdf
7. Strachan I, Greener M. Medication-related swallowing difficulties may be more common than we realise. *Pharmacy in Practice* 2005; **15** (9): 411–414.
8. Office for National Statistics. *Births and deaths in England and Wales, 2010*. London: ONS, 2011. Available at: www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2010/index.html
9. NHS Business Services Authority. *Prescribing of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs) - prescribing guidance and discussion points*. PCT Prescribing Report, November 2009. Available at: www.nhsbsa.nhs.uk/Documents/PPDPCTReports/pctreport_20092.pdf

Abbreviated Prescribing Information: Ramipril 2.5mg/5ml Oral Solution. Consult Summary of Product Characteristics before prescribing

Presentation: A clear colourless solution, each 5ml of solution contains 2.5mg Ramipril. **Therapeutic Indications:** Treatment of hypertension. Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with: manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or diabetes with at least one cardiovascular risk factor. Treatment of renal disease: Incipient glomerular diabetic nephropathy as defined by the presence of macroalbuminuria, manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor, manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day. Treatment of symptomatic heart failure. Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction. **Posology:** Ramipril Oral Solution should be taken each day at the same time. Depending on the indication and the patient the dosage ranges from 1.25mg (2.5ml) initially up to a maximum daily dosage of 10mg (20ml). **Paediatric population:** Use is not recommended. **Contra-indications:** Hypersensitivity to ramipril, to any of the excipients or any other ACE inhibitors, history of angioedema, extracorporeal treatments leading to contact of blood with negatively charged surfaces, bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney, 2nd and 3rd trimester of pregnancy. Do not use in patients with hypotensive or haemodynamically unstable states. **Precautions: Special populations** *Pregnancy:* Ramipril should not be initiated during pregnancy. Unless essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatment. When pregnancy is diagnosed, treatment should be stopped immediately, and, if appropriate, alternative therapy should be started. Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase. Medical supervision is necessary. Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload). Transient or persistent heart failure post MI. Patients at risk of cardiac or cerebral ischemia in case of acute hypotension. It is recommended that treatment with Ramipril should be discontinued where possible one day before surgery. Renal function should be assessed before and during treatment and dosage adjusted and where there is renal impairment. There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant. In case of angioedema during treatment, Ramipril must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours. Intestinal angioedema has been reported in patients treated with Ramipril. The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. Consider temporary discontinuation of Ramipril prior to desensitization. Hyperkalaemia has been observed in some patients treated with Ramipril. Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. ACE inhibitors cause higher rate of angioedema in black patients than in non black patients. Ramipril may be less effective in lowering blood pressure in black people than in non black patients. Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. **Excipient warnings:** contains ethyl hydroxybenzoate (E214) and butyl hydroxybenzoate which may cause allergic reactions. **Drug interactions:** Contra-indicated combinations: Extracorporeal treatments leading to contact of blood with negatively charged surfaces due to increased risk of severe anaphylactoid reactions. **Precautions for use:** Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances as hyperkalaemia may occur. Antihypertensive agents and other substances that may decrease blood pressure as potentiation of the risk of hypotension is to be anticipated. Vasopressor sympathomimetics and other substances that may reduce the antihypertensive effect of Ramipril: Blood pressure monitoring is recommended. Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell counts as there is an increased likelihood of haematological reactions. Excretion of lithium may be reduced therefore lithium levels must be monitored. Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended. Non-steroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of Ramipril is to be anticipated. Concomitant treatment of ramipril and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia. **Pregnancy and lactation:** Use is not recommended during the first trimester of pregnancy and contraindicated during the 2nd and 3rd trimesters of pregnancy. ACE inhibitor/ Angiotensin II Receptor Antagonist exposure during the 2nd and 3rd trimesters is known to induce human fetotoxicity and neonatal toxicity. The use of ramipril during breastfeeding is not recommended. **Effects on ability to drive and use machines:** Some adverse effects may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance. This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours. **Undesirable effects:** Common: Headache, dizziness, non-productive tickling cough, bronchitis, sinusitis, dyspnoea, gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting, rash in particular maculo-papular, muscle spasms, myalgia, blood potassium increased, hypotension, orthostatic blood pressure decreased, syncope, chest pain, fatigue. Uncommon: Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral, eosinophilia, vertigo, paraesthesia, ageusia, dysgeusia, visual disturbance including blurred vision, bronchospasm including asthma aggravated, nasal congestion, pancreatitis, pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth, renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased, angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis, arthralgia, anorexia, decreased appetite, flushing, pyrexia, hepatic enzymes and/or bilirubin conjugated increased, transient erectile impotence, libido decreased , depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence. Rare: White blood cell count decreased, red blood cell count decreased, haemoglobin decreased, platelet count decreased, tremor, balance disorder, conjunctivitis, hearing impaired, tinnitus, glossitis, exfoliative dermatitis, urticaria, onycholysis, vascular stenosis, hypoperfusion, vasculitis, asthenia, jaundice cholestatic, hepatocellular damage, confusional state. Very Rare: Photosensitivity reaction. Unknown: Bone marrow failure, pancytopenia, haemolytic anaemia, cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia, aphthous stomatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia, blood sodium decreased, Raynaud's phenomenon, anaphylactic or anaphylactoid reactions, antinuclear antibody increased, acute hepatic failure, cholestatic or cytolytic hepatitis, gynaecomastia, disturbance in attention. **Overdose:** Treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including administration of alpha 1 adrenergic agonists/angiotensin II. **Shelf Life and Storage:** Closed: 12 months, after first opening: 1 month. Store in a refrigerator (2-8°C). **Legal Category:** POM. **Pack Size and NHS Price:** 150ml - £80.00. **Marketing Authorisation Holder:** Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE. **Marketing Authorisation Number:** PL 00427/0162. **Date of Preparation:** March 2014.

Information about adverse event reporting can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to Rosemont Pharmaceuticals Ltd on 0113 244 1400