Medicines Management Programme:
Preferred Drugs

Angiotensin-Converting Enzyme (ACE) Inhibitors

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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Table of contents

1. Purpose ..................................................................................................................... 1
2. Definitions ................................................................................................................ 1
3. Preferred ACE inhibitor .......................................................................................... 2
4. Rationale for selection ............................................................................................ 2
  4.1 Licensed Therapeutic Indications .......................................................................... 2
  4.2 Clinical outcome data ......................................................................................... 3
  4.3 Clinical guidelines ............................................................................................... 4
  4.4 Cost ....................................................................................................................... 6
  4.5 Patient factors ...................................................................................................... 7
  4.6 Prescribing trends in Ireland .............................................................................. 8
5. Summary .................................................................................................................. 9
6. References ............................................................................................................... 10
7. Bibliography .......................................................................................................... 15
Appendix - Prescribing Tips for Ramipril ................................................................... 17

List of tables

Table 1. Licensed Indications & Frequency of Administration ...................................... 2
Table 2 Examples of pivotal ACE inhibitor RCTs reviewed in the selection process ...... 3
Table 3. Clinical Guidelines ........................................................................................ 5
Table A1. Ramipril dosing and administration ............................................................ 17

Table of figures

Figure 1. Reimbursement cost per month based on DDD. .............................................. 6
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCF</td>
<td>American College of Cardiology Foundation</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>BD</td>
<td>‘bis die’ – twice daily</td>
</tr>
<tr>
<td>BHS</td>
<td>British Hypertension Society</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>GMS</td>
<td>General Medical Services</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence (UK)</td>
</tr>
<tr>
<td>MMP</td>
<td>Medicines Management Programme</td>
</tr>
<tr>
<td>RAS</td>
<td>Renin-aldosterone system</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
</tbody>
</table>
1. Purpose

There are ten licensed angiotensin-converting enzyme (ACE) inhibitors in Ireland.¹ Annual expenditure on ACE inhibitors under the General Medical Services (GMS) scheme exceeds €15 million.²

The selection of a preferred ACE inhibitor under the Medicines Management Programme (MMP) is designed to support prescribers in choosing a medicine of proven safety and efficacy in the management of patients with cardiovascular conditions, particularly hypertension and heart failure. In selecting a preferred ACE inhibitor the MMP aims to enhance the quality of prescribing and provide value for money. Prescribers are encouraged to consider the preferred drug when initiating an ACE inhibitor, and when switching from another ACE inhibitor when a change in drug treatment is indicated.

The guidance may not be applicable to all patient populations, e.g. children and patients with congenital cardiac conditions, in which circumstances specialist advice may be sought. The use of ACE inhibitors is not recommended during the first trimester of pregnancy. ACE inhibitors are contraindicated during the second and third trimesters of pregnancy.³-¹²

2. Definitions

For the purposes of this report the associated cost refers to the reimbursed cost of the named ACE inhibitor as listed on the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS) website. Only licensed, reimbursed ACE inhibitors are included in this review. Where two or more preparations of the same drug are listed (e.g. where there are different manufacturers/suppliers), the least expensive preparation has been selected for the evaluation. Costs are correct as of July 2014.
3. Preferred ACE inhibitor

Under the MMP, the preferred ACE inhibitor is **RAMIPRIL**

4. Rationale for selection

4.1 Licensed Therapeutic Indications

A broad licence in terms of therapeutic indication(s) relative to other drugs in this class is considered advantageous. This enables the prescriber to use the same drug across a range of therapeutic indications. As the focus of this guidance is the use of ACE inhibitors for hypertension and heart failure, the preferred ACE inhibitor should be licensed at minimum for these two indications. Additional licensed therapeutic indications incorporating other patient groups, e.g. renal disease, are welcome. Captopril, lisinopril and ramipril are noted to have broad licences in terms of therapeutic indications relative to other drugs within the ACE inhibitor class, as demonstrated in table 1.

Table 1. Licensed Indications & Frequency of Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>HTN</th>
<th>HF</th>
<th>Renal disease/ nephropathy</th>
<th>Acute MI</th>
<th>Coronary heart disease</th>
<th>Frequency of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Once daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Three times daily</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Once daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>Once daily-BD</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Once daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>Once daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Once daily -BD</td>
</tr>
<tr>
<td>Ramipril</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Once daily-BD</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>✓</td>
<td>✓*</td>
<td></td>
<td></td>
<td>✓</td>
<td>Once daily-BD</td>
</tr>
<tr>
<td>Zofenopril</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Once daily</td>
</tr>
</tbody>
</table>

*Left ventricular dysfunction after myocardial infarction ± symptoms of heart failure ± residual ischaemia.11

Ramipril has the broadest licence in terms of therapeutic indications relative to other drugs within the ACE inhibitor class.
4.2 Clinical outcome data

The safety and efficacy of the preferred ACE inhibitor should be demonstrated in high quality randomised controlled trials (RCTs) and other published studies. Table 2 lists examples of the RCTs considered in the review process. This list is not exhaustive and is intended to serve as an example only. For the full list of RCTs and clinical studies considered as part of the review process, as well as submissions from relevant stakeholders, please see the bibliography.

Table 2. Examples of pivotal ACE inhibitor RCTs reviewed in the selection process

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pivotal Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>Pool J et al (2001)(^\text{13}); ACCOMPLISH (2008)(^\text{14})</td>
</tr>
<tr>
<td>Captopril</td>
<td>SAVE (1992)(^\text{15}); CAPP (1999)(^\text{16})</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>Cilazapril-Captopril Multicenter Group (1995)(^\text{17})</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>ATLAS (1999)(^\text{21}); ALLHAT (2002)(^\text{22})</td>
</tr>
<tr>
<td>Perindopril</td>
<td>PROGRESS (2001)(^\text{23}); EUROPA (2003)(^\text{24}); PEP-CHF Study (2006)(^\text{25}); PREAMI (2006)(^\text{26})</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Holt et al (1986)(^\text{27}); QUIET (1999)(^\text{28})</td>
</tr>
<tr>
<td>Ramipril</td>
<td>AIRE (1993)(^\text{29}); HOPE (2000)(^\text{30}); AASK (2002)(^\text{31})</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>TRACE (1995)(^\text{32})</td>
</tr>
<tr>
<td>Zofenopril</td>
<td>SMILE (1995)(^\text{33}); SMILE-2 (2003)(^\text{34}); SMILE-ISCHAEMIA (2007)(^\text{35})</td>
</tr>
</tbody>
</table>

Observational studies, meta-analyses and review articles were also considered as part of the review process. These were identified in the course of a search of the databases Medline (1946-2013), EMBASE (1974-2013) and International Pharmaceutical Abstracts (1970-2013).

Key findings are as follows:

- In an expert consensus document on ACE inhibitors in cardiovascular disease, the European Society of Cardiology (2004) state that ‘all currently available ACE inhibitors can be considered equally effective at lowering blood pressure’.\(^\text{36}\)

- In a comparison of ACE inhibitors for the treatment of congestive heart failure, Tu et al (2005) found that ‘relative to those initiated on enalapril, no significant differences in the combined end point of re-admission to the hospital for congestive heart failure or mortality were observed among users of lisinopril, ramipril, or other ACE inhibitors (included benazepril, captopril, cilazapril, fosinopril, perindopril, quinapril, and trandolapril)’.\(^\text{37}\)
• A Cochrane review (2008) of the blood pressure lowering efficacy of ACE inhibitors for primary hypertension found that ‘there are no clinically meaningful BP-lowering differences between different ACE inhibitors’. 38

• The National Institute for Health and Care Excellence (NICE) Guideline Development Group (UK) assumed a drug class effect when assessing results of studies of ACE inhibitors. 39

On this basis the MMP considers all ACE inhibitors to have similar efficacy in terms of BP-lowering effects and in heart failure.

ACE inhibitors are considered to have similar efficacy in terms of BP-lowering effects and in heart failure.

4.3 Clinical guidelines

In the absence of clinical guidelines specific to Ireland, international clinical guidelines on the management of hypertension and heart failure were considered in the process of identifying the ACE inhibitor of choice (table 3). In some clinical guidelines, particular ACE inhibitors are preferred; in many cases, no preference is given for a particular drug but certain drug properties are considered favourable, e.g. generic drug, once daily administration.

Submissions from clinicians with a special interest in the relevant therapeutic areas were also considered in the process.
### Table 3. Clinical Guidelines

<table>
<thead>
<tr>
<th>Group</th>
<th>Guideline</th>
<th>Year</th>
<th>Preferred ACE inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Society of Cardiology (ESC) 40, 41</td>
<td>Heart failure</td>
<td>2012</td>
<td>Captopril, enalapril, lisinopril, ramipril, trandolapril (41)</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE) Clinical Guideline No. 108 42</td>
<td>Heart failure</td>
<td>2010</td>
<td>Not specified</td>
</tr>
<tr>
<td>American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 43</td>
<td>Heart failure</td>
<td>2009</td>
<td>Not specified</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guideline Network (SIGN) 44</td>
<td>Heart failure</td>
<td>2007</td>
<td>Not specified</td>
</tr>
<tr>
<td>European Society of Cardiology (ESC) 45</td>
<td>Hypertension</td>
<td>2013</td>
<td>Not specified</td>
</tr>
<tr>
<td>British Hypertension Society (BHS) IV 47</td>
<td>Hypertension</td>
<td>2004</td>
<td>Not specified. Generic, once daily.</td>
</tr>
</tbody>
</table>

### Practice guidelines

| National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary (CKS) 48 | Heart failure | 2010 | Enalapril, lisinopril, ramipril, trandolapril. |
| National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary (CKS) 59 | Hypertension (not diabetic) | 2012 | • HTN: Enalapril, lisinopril, ramipril.  
• HTN + HF: Enalapril, lisinopril, ramipril, trandolapril. 
• Diabetes + HTN: As for HTN + HF - & perindopril  
• HTN + MI: Lisinopril, perindopril, ramipril. |

Ramipril is among the ACE inhibitors recommended for the treatment of hypertension and heart failure in a number of international clinical guidelines.
4.4 Cost

Value for money is an important consideration. A drug of lower acquisition cost is preferred, notwithstanding safety and efficacy data, i.e. the cheaper of two drugs is preferred unless the more expensive has a proven advantage.\textsuperscript{49}

Optimal dose and frequency of administration were important factors for consideration in terms of cost, i.e. the daily cost of treating a patient with the optimal dose at the correct dosing frequency was considered. The optimal dose was obtained from the Summary of Product Characteristics (SmPCs),\textsuperscript{3-12} the British National Formulary\textsuperscript{50} and where available, clinical guidance.\textsuperscript{41} Ramipril is considered to have a favourable cost profile relative to other ACE inhibitors.\textsuperscript{2}

Figure 1 displays the typical reimbursement cost per month of available ACE inhibitors based on the defined daily dose (DDD) or its nearest available tablet strength.\textsuperscript{51}

Figure 1. Reimbursement cost per month based on DDD.

Ramipril has a favourable cost profile across all doses and frequencies relative to other ACE inhibitors.
4.5 Patient factors

4.5.1 Dosing and Administration
In the absence of clinical outcome data demonstrating superiority of one drug over another, drugs taken once daily are preferred to those requiring multiple daily doses. This was not particularly relevant in the case of ACE inhibitors where the majority are taken once daily (table 1). Captopril is generally administered three times a day.\textsuperscript{4, 50}

4.5.2 Adverse effects
The preferred drug should not carry a high risk of adverse effects or drug interactions relative to other drugs in its class.\textsuperscript{49} Licensed product information (SmPCs), the BNF and clinical reviews do not suggest significant differences in adverse effect profiles between ACE inhibitors. The results of a meta-analysis of almost 200,000 patients treated with ACE inhibitors suggest that the incidence of cough is similar among all ACE inhibitors and may be several-fold higher in the literature than reported in product information and RCTs.\textsuperscript{52} Therefore, the MMP considers the ACE inhibitors similar in terms adverse effect profiles.

4.5.3 Cost to patients
Cost is also an important consideration for patients; a drug of lower acquisition cost is preferred, bearing in mind optimum dosage and frequency of administration. Ramipril and lisinopril are considered to have favourable cost profiles relative to other ACE inhibitors across all doses and frequencies.\textsuperscript{2}

With the exception of captopril, which is given three times a day, there are no significant differences between ACE inhibitors in terms of administration & adverse effect profiles.
Ramipril has a favourable cost profile across all doses and frequencies relative to other ACE inhibitors.
4.6 Prescribing trends in Ireland

Current prescribing data for ACE inhibitors in single agent and combination products were considered in the selection process. Approximately 85% of ACE inhibitors prescribed on the GMS scheme in Ireland are prescribed as single agent products.\(^5\) Of these, ramipril is the most frequently prescribed ACE inhibitor, followed by perindopril and lisinopril, respectively.\(^5\)

Ramipril is the most frequently prescribed ACE inhibitor in Ireland.
5. Summary

Preferred ACE inhibitor: RAMIPRIL

- Ramipril has the broadest licence in terms of therapeutic indications relative to other drugs within the ACE inhibitor class.
- On the basis of available evidence, ACE inhibitors are considered to have similar efficacy in terms of BP-lowering effects and in heart failure.
- Ramipril is listed as a suitable ACE inhibitor in a number of international clinical guidelines on the management of hypertension and heart failure.
- Ramipril is considered to have a favourable cost profile across all doses and frequencies relative to other ACE inhibitors.
- There are no significant differences between ACE inhibitors in terms of administration and adverse effect profiles.
- Ramipril is the most frequently prescribed ACE inhibitor in Ireland.
6. References


26. The PREAMI Investigators. Effects of Angiotensin-Converting Enzyme Inhibition with Perindopril on Left Ventricular Remodelling and Clinical Outcome: Results of the
Randomized Perindopril and Remodelling in Elderly with Acute Myocardial Infarction (PREAMI) Study. *Archives of Internal Medicine* 2006; 166: 659-666.


7. Bibliography


10. MSD. Correspondence 7th August 2013. Renitec® (enalapril) 5 mg and 20 mg tablets: Summary of Human Pharmacological and Clinical Data. 7th August 2013. On file.


Appendix.

Prescribing Tips for Ramipril

There is a range of ramipril preparations available. An up-to-date listing is freely available on the Health Products Regulatory Authority (HPRA) website at [www.hpра.ie](http://www.hpра.ie).

Therapeutic Indications
- Hypertension
- Heart failure
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in high risk patients, including diabetes
- Renal disease/nephropathy
- Secondary prevention after myocardial infarction

Dosing and Administration
Full prescribing information is available in the Summary of Product Characteristics (SmPC) which may be accessed freely online at [www.hpра.ie](http://www.hpра.ie) and [www.medicines.ie](http://www.medicines.ie). Please consult the SmPC for guidance on prescribing in special patient populations, e.g. renal impairment, and in conditions other than hypertension and heart failure.

Table A1. Ramipril dosing and administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial Dose</th>
<th>Titration &amp; Maintenance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.5 mg once daily</td>
<td>Double the dose every 2-4 weeks to max. 10 mg once daily.</td>
<td>Patients with strongly activated RAS may require lower starting dose, i.e. 1.25 mg.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.25 mg once daily</td>
<td>Double the dose every 1-2 weeks to maximum of 10 mg daily in 1-2 doses.</td>
<td></td>
</tr>
</tbody>
</table>

**DOSE** Prescribe the correct dose and frequency for the patient’s condition – see SmPC for details.
- **Hypertension**: start with 2.5 mg once daily
- **Heart failure**: start with 1.25 mg once daily
- **Up-titrate** by doubling the dose at appropriate intervals

**OPTIMISE** Patients benefit from higher doses when tolerated.

**MONITOR**
- **Renal function** – serum creatinine and electrolytes should be checked before starting treatment, 1-2 weeks after each dose increase and at least annually, thereafter.39
- **BP** – ACE inhibitors can cause profound hypotension, particularly after the first dose. Patients at increased risk include those with heart failure, those taking concomitant diuretics, on a low-sodium diet, on dialysis and suffering from dehydration.
- **Cough** – a persistent dry cough occurs in 10-15% of patients treated with an ACE inhibitor.

**TARGET**
- In most patients the **target SBP is <140 mmHg**. A **DBP target of <90 mmHg** is always recommended, except in patients with **diabetes**, in whom values **<85 mmHg** are recommended.45
- In elderly patients with an initial SBP >160 mmHg, a reduction to 140-150 mmHg may be considered.

Further advice on BP targets is accessible via NICE ([www.nice.org.uk](http://www.nice.org.uk)) and through the ESC website ([www.escardio.org](http://www.escardio.org)).