Medicines Management Programme:

Preferred Drugs

Angiotensin-Converting Enzyme (ACE) Inhibitors

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Table of contents

List of tables

Table of figures

List of abbreviations

ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
AHA	American Heart Association
BD	*'bis die'* – twice daily
BHS	British Hypertension Society
BP	Blood pressure
CHF	Congestive heart failure
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
GMS	General Medical Services
HF	Heart failure
HTN	Hypertension
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence (UK)
MMP	Medicines Management Programme
RAS	Renin-aldosterone system
RCT	Randomised controlled trial
SBP	Systolic Blood Pressure

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

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

*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

Drug	***Pivotal Trials***
Benazepril	Pool J *et al* (2001)[13]; ACCOMPLISH (2008) [14]
Captopril	SAVE (1992)[15] ; CAPP (1999)[16]
Cilazapril	Cilazapril-Captopril Multicenter Group (1995)[17]
Enalapril	CONSENSUS (1987)[18]; SOLVD (1991)[19]; ABCD (1998)[20]
Lisinopril	ATLAS (1999)[21]; ALLHAT (2002)[22]
Perindopril	PROGRESS (2001)[23]; EUROPA (2003)[24]; PEP-CHF Study (2006)[25]; PREAMI (2006)[26]
Quinapril	Holt *et al* (1986)[27]; QUIET (1999) [28]
Ramipril	AIRE (1993)[29]; HOPE (2000)[30] ; AASK (2002) [31]
Trandolapril	TRACE (1995) [32]
Zofenopril	SMILE (1995)[33]; SMILE-2 (2003)[34]; SMILE-ISCHAEMIA (2007) [35]

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'.* [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)'.[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

Group	***Guideline***	***Year***	***Preferred ACE inhibitor***
European Society of Cardiology (ESC) [40, 41]	Heart failure	2012	Captopril, enalapril, lisinopril, ramipril, trandolapril [(41)]
National Institute for Health and Care Excellence (NICE) Clinical Guideline No. 108 [42]	Heart failure	2010	Not specified
American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [43]	Heart failure	2009	Not specified
Scottish Intercollegiate Guideline Network (SIGN) [44]	Heart failure	2007	Not specified
European Society of Cardiology (ESC) [45]	Hypertension	2013	Not specified
National Institute for Health and Care Excellence (NICE) Clinical Guideline No. 127 [46]	Hypertension	2011	Not specified. Generic, once daily.
British Hypertension Society (BHS) IV [47]	Hypertension	2004	Not specified Generic, once daily.
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) [39]	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.[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), [3-12] the British National Formulary [50] and where available, clinical guidance.[41] Ramipril is considered to have a favourable cost profile relative to other ACE inhibitors.[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.[51]

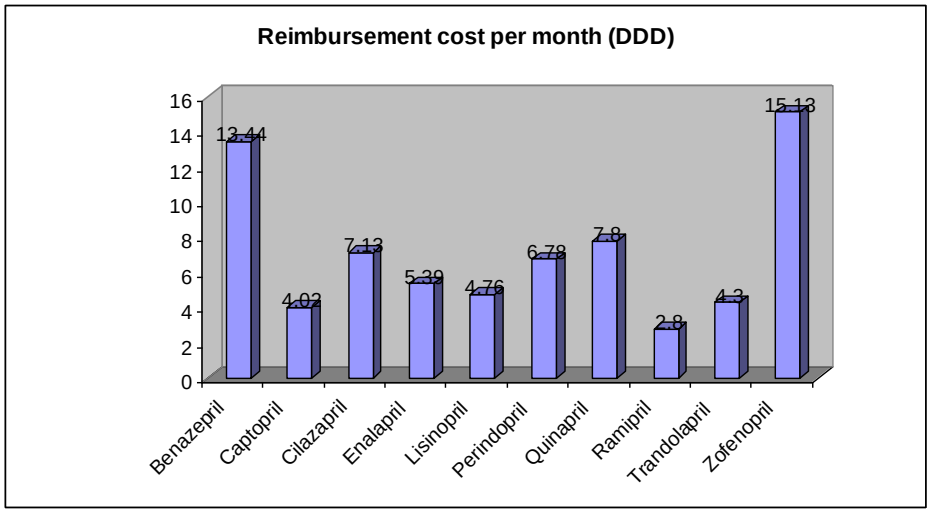

Figure 1. Reimbursement cost per month based on DDD.

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). [3, 5-12] Captopril is generally administered three times a day.[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.[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.[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. [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.[53] Of these, ramipril is the most frequently prescribed ACE inhibitor, followed by perindopril and lisinopril, respectively.[53]

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.

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Preferred Drugs
THE RIGHT CHOICE, RIGHT NOW.
MEDICINES MANAGEMENT PROGRAMME

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.hpra.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.hpra.ie and 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

Indication	Initial Dose	Titration & Maintenance	Comment
Hypertension	2.5 mg once daily	Double the dose every 2-4 weeks to max. 10 mg once daily.	Patients with strongly activated RAS may require lower starting does, i.e. 1.25 mg.
Heart failure	1.25 mg once daily	Double the dose every 1-2 weeks to maximum of 10 mg daily in 1-2 doses.	

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) and through the ESC website (www.escardio.org).