Medicines Management Programme:

Preferred Drugs

Angiotensin-II receptor blockers (ARBs)

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List of Abbreviations

ACE	Angiotensin converting enzyme
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ARB	Angiotensin-II receptor blocker
BHS	British Hypertension Society
BD	*'bis die'* – twice daily
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
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence (UK)
MMP	Medicines Management Programme
RCT	Randomised controlled trial
SBP	Systolic blood pressure

1. Purpose

There are eight licensed angiotensin-II receptor blockers (ARBs) available in Ireland.[1] Annual expenditure on ARBs under the General Medical Services (GMS) scheme is approximately €25 million.[2]

The selection of a preferred ARB 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, in particular hypertension and heart failure. GMS data suggest that ARBs may not be optimally prescribed nationally.[3] In selecting a preferred ARB the MMP aims to enhance the quality of prescribing and provide value for money.

The guidance may not be applicable to all patient populations, e.g. children and patients with congenital cardiac conditions, in which circumstances specialist advice should be sought. The use of ARBs is not recommended during the first trimester of pregnancy. The use of ARBs is contraindicated during the second and third trimesters of pregnancy.[4-11]

2. Definitions

For the purposes of this report the associated cost refers to the reimbursed cost of the named ARB as listed on the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS) website. Only licensed, reimbursed ARBs 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 ARB

Under the MMP, the preferred ARB is CANDESARTAN.

4. Rationale for selection

4.1 Licensed Indications

A broad licence in terms of therapeutic indication(s) relative to other drugs in this class is considered advantageous. As the focus of this guidance is the use of ARBs in hypertension and heart failure, the preferred ARB should be licensed at minimum for these two indications. Additional licensed therapeutic indications incorporating other patient groups, e.g. renal disease, are welcome.

All eight ARBs are licensed for the treatment of hypertension.[4-11] Three ARBs, candesartan, losartan and valsartan, are also indicated in heart failure.[5,8,11] These differences in the licensing particulars were considered significant in enabling our recommendation for a single agent ARB product.

Among the three named ARBs, there exist additional differences in terms of licensed indications. Losartan has the broadest licence in terms of therapeutic indications, followed by valsartan (table 1).

Table 1. Licensed Indications & Frequency of Administration [4-11]

Drug	HTN	HF	Renal disease* (diabetes)	Recent MI	Reduction of stroke risk in LVH	Cardiovascular prevention	Frequency of Admin.
Azilsartan	✓						Once daily
Candesartan	✓	✓					Once daily
Eprosartan	✓						Once daily
Irbesartan	✓		✓				Once daily
Losartan	✓	✓	✓		✓		Once daily
Olmesartan	✓						Once daily
Telmisartan	✓					✓	Once daily
Valsartan	✓	✓		✓			HTN: once daily HF/MI: BD

All licensed ARBs are indicated for the treatment of hypertension. Candesartan, losartan & valsartan are also licensed in heart failure. A broader licence enables prescribers to use the same drug across a range of therapeutic indications.

4.2 Clinical outcome data

The safety and efficacy of the preferred drug 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 papers considered as part of the review process, as well as submissions from relevant stakeholders, please see the bibliography.

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

Drug	***Pivotal Trials***
Azilsartan	White *et al* (2011)[12]; Sica *et al* (2011)[13]
Candesartan	STRETCH (1999)[14]; SPICE (2000)[15]; CHARM Overall (2003)[16]; CHARM Alt (2003)[17]; CHARM Added (2003)[18]; SCOPE (2003)[19]
Eprosartan	Eprosartan Study Group (1999)[20]; ADEPT (2001)[21]
Irbesartan	IDNT (2001)[22]
Losartan	ELITE (1997)[23]; ELITE II (2000)[24]; LIFE (2000)[25,26]; RENAAL (2001)[27]; OPTIMAAL (2002)[28]; HEALL (2009)[29]
Olmesartan	Oparil *et al* (2001)[30]; Stumpe KO *et al* (2002)[31]; Brunner *et al* (2003)[32]; ESPORT (2010)[33]
Telmisartan	TRANSCEND (2008)[34]; ONTARGET (2008)[35]
Valsartan	Val-HeFT (2001)[36]; HEAVEN (2002)[37]; VALIANT (2003)[38]; VALUE (2004)[39]

The following points summarise some of the main trial findings:

4.2.1 Azilsartan

- Azilsartan was first licensed in Europe in 2011.[4] It has been compared to placebo, olmesartan and valsartan in clinical trials. [12, 13] However, the beneficial effects of azilsartan on mortality and cardiovascular morbidity and target organ damage are currently unknown.[4]
- Azilsartan is not licensed for heart failure.[4]

4.2.2 Candesartan

- In the CHARM-Alternative trial (n=2028), candesartan significantly reduced cardiovascular death and hospital admissions for heart failure in patients with congestive heart failure (CHF) unable to tolerate an angiotensin-converting enzyme (ACE) inhibitor compared to placebo (adjusted hazard ratio for cardiovascular death or hospital admission for CHF 0.70, p<0·0001). In this trial, the mean dose of candesartan taken by patients with CHF at 6 months was 23 mg daily.[17]
- In the SCOPE study (n=4964) candesartan-based therapy (mean dose 11.6±4 mg), in combination with standard antihypertensives, resulted in a slightly greater blood pressure reduction compared with placebo therapy. It was associated with a modest, statistically non-significant, reduction in major cardiovascular events and with a significant reduction in non-fatal stroke.[19]
- In the STRETCH study (n=844) candesartan 16 mg daily produced a significant improvement in exercise tolerance among patients with CHF compared to placebo. Doses of 4 mg, 8 mg and 16 mg candesartan significantly improved symptoms of dyspnoea relative to placebo.[14]

4.2.3 Eprosartan

- The ADEPT trial (n=36) demonstrated that when added to an ACE inhibitor, eprosartan (200 mg twice daily) significantly reduced blood pressure (BP) compared with placebo.[21] In patients with mild-moderate essential hypertension (n=243), eprosartan 600 mg once daily was shown to produce statistically significant reductions in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to placebo. [20]
- In a RCT comparing eprosartan 200 mg twice daily to enalapril 10 mg daily in hypertensive patients (n=118), the mean change in DBP in Caucasian patients was greater with eprosartan than enalapril. Eprosartan was more effective at lowering SBP in patients < 65 years, females and Caucasians, and in patients with a baseline DBP < 120 mm Hg or not receiving a thiazide at baseline.[40]
- Eprosartan is not licensed for the treatment of heart failure.

4.2.4 Irbesartan

- In the IDNT trial (2001) (n=1715) irbesartan was more effective in protecting against the development of diabetic nephropathy than amlodipine and placebo.[22] Irbesartan caused a greater reduction in mean BP compared to placebo and similar reduction in BP compared to amlodipine.
- Eprosartan is not licensed for the treatment of heart failure.

4.2.5 Losartan

Losartan was the first of the ARB class licensed and its suitability as an alternative to an ACE inhibitor in cases of intolerance was established in RCTs. However, there is concern that the optimal dose of losartan has not been established, particularly in heart failure.[41]

- In the LIFE study (n=9193), losartan produced similar reductions in BP to atenolol (across a similar dose range) though cardiovascular morbidity and mortality were significantly reduced. The mean dose taken by those who completed the study was 82 mg daily.[26]
- In the ELITE II trial (n=3152), losartan 50 mg daily was not better than captopril 50 mg three times a day in improving survival in elderly patients with chronic heart failure.[24]
- A target dose of losartan 150 mg/day has been shown to be significantly more effective in preventing cardiovascular death, cardiovascular admission or heart failure admission than a lower dose of 50 mg daily for heart failure. [29]

4.2.6 Olmesartan

A number of studies have suggested that olmesartan may produce greater and/or more sustained reductions in SBP and DBP compared to other ARBs.

- Brunner *et al* (2003) conducted an eight week study (n=643) in which patients with essential hypertension received either olmesartan 20 mg or candesartan 8 mg daily. The mean decreases in BP from baseline were significantly greater with olmesartan than candesartan for DBP and SBP.[32] Of note, olmesartan 20 mg is considered the optimal dose in hypertension[9] where as candesartan 8mg is the recommended starting dose for hypertension.[5]
- Stumpe *et al* (2002) compared the blood pressure-lowering effects of olmesartan 10 mg to losartan 50 mg in patients with mild-moderate hypertension (n=316). After 12 weeks of treatment olmesartan had induced a significantly greater reduction in both DBP and SBP compared to losartan.[31]
- In the ESPORT study (n=1102), which compared the BP-lowering efficacy of olmesartan (10-40 mg daily) and ramipril (2.5-10 mg daily) in elderly (≥65 years) hypertensive patients, the reduction in SBP and DBP achieved with olmesartan was greater than that achieved with ramipril. These differences reached statistical significance in the ≥65-69 years age group. In patients ≥70 years, the difference in the reduction in DBP between the two groups was statistically significant. The response rates were also significantly higher with olmesartan than with ramipril.[33]

While olmesartan has been shown to effectively lower BP, sometimes more effectively than other ARBs, an associated improvement in clinical outcomes has not yet been demonstrated in large RCTs, i.e. surrogate outcomes such as reduction in BP have been the primary outcomes in RCTs to date, as opposed to clinical outcomes (e.g. stroke, MI).

Olmesartan is not licensed for the treatment of heart failure.

4.2.7 Telmisartan

- The ONTARGET trial (n=25,620) compared telmisartan 80 mg daily, ramipril 10 mg daily and a combination of both in patients at high risk of vascular events. Telmisartan was non-inferior to ramipril at preventing death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure.[35]
- In the TRANSCEND study of patients with cardiovascular disease or diabetes with end organ damage intolerant to ACE inhibitors (n=5926), telmisartan 80 mg was compared to placebo. Telmisartan resulted in a greater overall reduction in BP compared to placebo, which was sustained throughout the study. Telmisartan had no significant effect on the primary outcome, which included hospitalisations for heart failure, but modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke. Telmisartan did not reduce the risk of new onset diabetes.[34]
- Telmisartan is not licensed for the treatment of heart failure.

4.2.8 Valsartan

- In the VALUE study (n=15,245), which looked at outcomes in hypertensive patients at high cardiovascular risk taking amlodipine-based and valsartan-based regimens, the median dose of valsartan used was 151.7 mg daily.[39] Amlodipine-based therapy (mean dose 8.5 mg daily) was significantly more effective than valsartan-based therapy at lowering the BP, especially during the early stages of treatment.
- In the ValHeFT trial (n=5010), the addition of valsartan (mean dose 254 mg given in two divided doses) to standard therapy for heart failure demonstrated some benefit in the combined end point of mortality and morbidity compared to placebo, predominantly because of fewer hospital admissions for heart failure in the valsartan group.[36]
- The VALIANT trial (n=14703) demonstrated that valsartan (at a target dose of 160 mg twice daily) was as effective as captopril in preventing death from any cause, death from cardiovascular causes, and reducing cardiovascular morbidity in high risk patients following MI.[38]

4.2.9 Comparative efficacy

Observational studies, meta-analyses and review articles were considered in the review process. These were obtained in the course of a search of the databases Medline (1946-2013), EMBASE (1974-2013) and International Pharmaceutical Abstracts (1970-2013). A number of clinical reviews and meta-analyses of ARBs have been undertaken, with varying results:

4.2.9.1 Hypertension

- A meta-analysis of the antihypertensive efficacy of ARBs as monotherapy found that the blood pressure reduction with losartan at starting and maximum dose was consistently inferior to other ARBs.[42]
- A Cochrane review (2008) of the blood pressure lowering efficacy of ARBs concluded that '*when the different ARBs are compared, there is a similarity in their BP lowering effects at trough . . . For many of the drugs, there are insufficient data for a full range of doses. . . It would require head-to-head trials of different ARBs at equivalent BP lowering doses to assess whether or not there are differences in the BP lowering efficacy between different drugs*.[43]

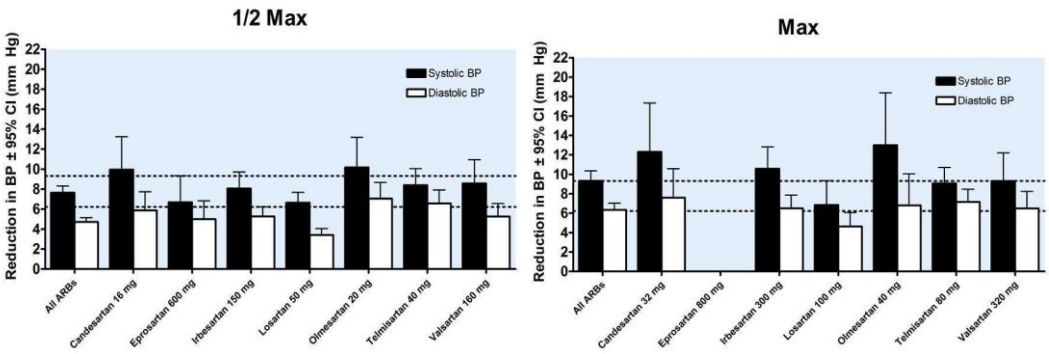

Figure 1. Blood pressure lowering efficacy of ARBs. [43]

4.2.9.2 Heart failure

- In a population study of ARBs in the treatment of heart failure, Hudson *et al* (2007) found that losartan resulted in poorer outcomes compared to valsartan, candesartan, irbesartan and telmisartan.[44]
- In a study of ARBs on mortality in heart failure, Desai *et al* (2012) concluded that losartan, candesartan, valsartan and irbesartan had similar effectiveness in reducing mortality in congestive heart failure (CHF) patients.[45]
- A Cochrane review of ARBs for heart failure (2012) concluded that '*there is no available RCT evidence that demonstrates that any individual ARB is more or less effective than another in the treatment of heart failure'*.[46]

4.2.9.3 Candesartan vs. losartan

A number of studies have compared the effects of candesartan and losartan on various outcomes:

- In a large observational study of Swedish electronic patient records (n=29,943), Russell *et al* found that in hypertensive patients without underlying cardiovascular disease treated with candesartan, the incidence of a first cardiovascular event was significantly lower compared to those treated with losartan.[47]
- In a Swedish heart failure registry study (n=5139) the use of candesartan was associated with a lower mortality risk at 1 and 5 years compared to losartan. [48]
- The CLAIM-II trial (n=611) determined that candesartan (16-32 mg) lowered the trough, peak and 48-hour post-dose BP significantly more effectively than losartan (50-100 mg), with similar response rates between the groups.[49]
- In a systematic review and meta-analysis of 12 trials comparing candesartan and losartan in the management of essential hypertension, Zheng *et al* (2011) concluded that candesartan was superior to losartan in reducing SBP and DBP across a range of doses (candesartan vs. losartan: 8 mg vs. 50 mg; 16 mg vs. 100 mg; 16 mg vs. 50 mg; 32 mg vs. 100 mg).[50]

4.2.9.4 Valsartan vs. losartan

- Hedner *et al* (1999) found that valsartan (80-160 mg) and losartan (50-100 mg) produced similar reductions in BP in a trial of hypertensive patients (n=1369) but that significantly more patients responded to valsartan at eight weeks.[51]
- In a small open-label study (n=40) of losartan 50 mg vs. valsartan 80 mg once daily, valsartan was more effective at controlling 24-hour ambulatory BP than losartan. Mean night time SBP and DBP were significantly lower with valsartan than losartan.[52]

4.2.9.5 Candesartan vs. valsartan

To our knowledge, there is no large RCT comparing the efficacy or clinical outcomes of candesartan vs. valsartan treatment in hypertension or heart failure.

- In a meta-analysis of 31 trials involving 13,110 patients, Nixon *et al* (2009) found that at doses of 160 mg and 320 mg, valsartan is more effective at reducing SBP and DBP than losartan 100 mg. At comparable doses, defined as candesartan 32 mg, irbesartan 300 mg, olmesartan 40 mg and telmisartan 80 mg, valsartan achieved comparable antihypertensive efficacy to the other ARBs.[53]
- In a small open label study (n=308) of the effects of candesartan (8 mg daily), telmisartan (40 mg daily) and valsartan (80 mg daily) on metabolic parameters in hypertensive patients with type 2 diabetes mellitus, patients experienced a significant reduction in SBP and DBP, which was comparable across all three groups.[54]

For hypertension, the evidence suggests that candesartan (and possibly valsartan) is more effective at lowering BP than losartan. There is no head-to-head RCT comparing the BP-lowering effects of candesartan and valsartan. For heart failure, the effects of candesartan and valsartan are comparable.

4.3 Clinical guidelines

In the absence of specific Irish guidance, international clinical guidelines for the management of hypertension and heart failure were considered in the selection process. In some clinical guidelines, particular ARBs are preferred over others; in many cases, no preference is given for a particular drug, but certain drug properties are considered favourable, e.g. 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 ARB
European Society of Cardiology [55, 56]	Heart failure*	2012	Candesartan, valsartan
National Institute of Health and Care Excellence (NICE) Clinical Guideline No. 108 [57]	Heart failure	2010	Not specified
American College of Cardiology Foundation/ American Heart Association [58]	Heart failure	2009	Not specified
European Society of Cardiology [59]	Hypertension	2013	Not specified
National Institute of Health and Care Excellence (NICE) Clinical Guideline No. 127 [60]	Hypertension	2011	Not specified. Prefer low cost, once daily administration, generic.
British Hypertension Society (BHS) IV [61]	Hypertension	2004	Not specified. Prefer low cost, once daily administration, generic.
Practice Guidelines			
National Institute of Health and Care Excellence (NICE) - Clinical Knowledge Summary [62]	Heart Failure	2010	Candesartan, losartan, valsartan.
National Institute of Health and Care Excellence (NICE) - Clinical Knowledge Summary [63]	Hypertension	2012	Essential HTN: losartan HTN + HF: candesartan, losartan, valsartan HTN + diabetes: candesartan, losartan, valsartan, irbesartan

**ESC Guidelines for the diagnosis and treatment of chronic heart failure* (2012) redirect to an ESC 2005 publication.[54]

Candesartan, losartan and valsartan are listed as suitable ARBs for the treatment of heart failure and hypertension in a number of international clinical guidelines on the treatment of hypertension and heart failure (table 3).

Candesartan is among the ARBs recommended in a number of international clinical guidelines on the management of hypertension and heart failure.

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.[64] Cost is also an important consideration for patients who pay for their medicines. Azilsartan, eprosartan, irbesartan, olmesartan and telmisartan are more expensive than the three remaining ARBs.[2]

Figure 2 displays the typical reimbursement cost per month based on the defined daily dose (DDD).[65] The DDD of azilsartan has not been established by the World Health Organisation (WHO) [66] and therefore, a typical dose of 40 mg was assumed based on the SmPC.[4]

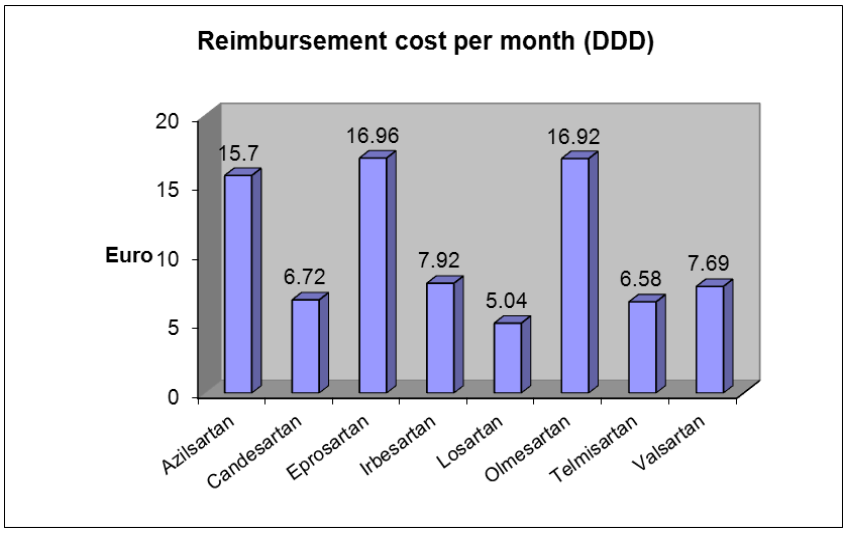

Figure 2. Typical reimbursement cost per month based on the DDD.

Optimal dose and frequency of administration were important factors for consideration in terms of cost. The ARBs candesartan, irbesartan, losartan, telmisartan and valsartan were considered to have a favourable cost profile on a '*per pack*' basis. However, the cost is influenced by the most efficacious dose and the dosing frequency. The clinical evidence presented suggests that higher doses of losartan may be required to achieve therapeutic response in patients with hypertension or heart failure, which impacts on the cost of treating these patients.

Valsartan is administered twice daily in heart failure and in patients post-MI, the target dose being 160 mg twice daily,[11] making valsartan one of the more expensive ARBs for heart failure. Candesartan is given once daily for both hypertension and heart failure[5] and the cost of treating a patient with the optimal dose is at least comparable to other ARBs.

Candesartan, which is given once daily for hypertension and heart failure, has a comparable or favourable cost profile relative to other ARBs, particularly taking into accounts factors such as frequency of administration and dose-response.

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. As discussed above in 'Cost' and in table 1, valsartan is administered twice daily in heart failure and once daily for hypertension.[11] Candesartan and losartan are taken once daily for both indications.[5, 8]

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 it class.[64] The relevant Summary of Product Characteristics (SmPCs), the British National Formulary (BNF) and various clinical reviews do not suggest significant differences between ARBs in terms of adverse

effect profiles. [4-11, 30, 42-44, 46, 53, 67] Therefore, the MMP considers ARBs equivalent in terms of incidence and severity of adverse effects.

4.5.3 Cost

Cost is an important consideration; a drug of lower acquisition cost is preferred while remaining cognisant of frequency of administration and dose-response (see section 3.4).

There are no significant differences between ARBs in terms of adverse effect profiles. Candesartan is considered to have a comparable or favourable cost profile across all doses and frequencies relative to other ARBs and is taken once daily for both hypertension and heart failure.

4.6 Prescribing trends in Ireland

Approximately 66% of ARBs prescribed under the GMS scheme are prescribed as single agent products. Valsartan is the most frequently prescribed single agent ARB followed by losartan.[3] In formulating the recommendation the importance of optimal dose and frequency of administration was considered.

Candesartan

- Candesartan is administered once daily in both hypertension and heart failure. The MMP believes that a once daily dosing frequency for all licensed indications is preferable.
- The target dose for patients with heart failure is 32 mg once daily.[5] In the CHARM-Alternative trial, the mean dose of candesartan taken by patients with chronic heart failure at 6 months was 23 mg daily.[17] GMS prescribing data indicate that approximately 35% of prescriptions for candesartan are for doses of 16 mg or higher, the majority of these being 16 mg.[3] This suggests that patients with heart failure may require higher doses than they currently receive in order to obtain the full benefits of candesartan therapy.

Losartan

Losartan is administered once daily in both hypertension and heart failure. However, as discussed under 'Clinical outcome data', there are concerns that the optimal dose of losartan has not been established;

- The results of the ELITEII, OPTIMALL and HEALL trials suggest that higher doses of losartan (≥ 100 mg daily) may be necessary for optimum therapeutic benefit in heart failure.
- A large Danish registry-based study (n=6479) of patients with heart failure found that compared with high doses of candesartan (16-32 mg), low-dose (12.5 mg) and medium-dose losartan (50 mg) were associated with increased mortality; use of high-dose losartan (100 mg) was similar in risk.[68]

In the LIFE study, losartan (mean daily dose: 82 mg) prevented more cardiovascular morbidity and death than atenolol in hypertensive patients.[26] The HEALL study determined that losartan 150 mg is significantly more effective at preventing cardiovascular death in patients with CHF than 50 mg.[29] In Ireland, 65% of prescriptions for losartan dispensed under the GMS scheme are for daily doses of 50 mg or less and very few patients are receiving 150 mg losartan daily, [3] again suggesting that many patients may not be receiving the full benefits of losartan therapy.

Valsartan

- Valsartan is administered once daily for hypertension and twice daily in heart failure and post-myocardial infarction.[11]
- Figures from the GMS prescribing database indicate that valsartan is very rarely prescribed twice daily in Ireland,[3] suggesting that in some heart failure patients, valsartan is not prescribed in line with its product licence. As discussed previously, adherence to the evidence-based recommendation of twice daily dosing with valsartan has cost implications.
- In the VALUE study the median dose of valsartan used for the treatment of hypertension was 151.7 mg daily.[39] In the VALIANT study, the target dose of valsartan was 160 mg BD; at one year the mean daily dose taken by patients was

247 mg ± 105 mg.[38] GMS data indicate that as few as one third of patients are prescribed this higher target dose[3] (nearest tablet strength: 160 mg) suggesting that many patients may be receiving sub-therapeutic doses for hypertension and following MI.

- 15% of GMS patients treated with Diovan® (valsartan) are receiving 40 mg,[3] a dose which in adults is indicated in heart failure and recent MI and should be given twice daily.[11] However, GMS data indicate that only 2.5% of patients on valsartan 40 mg are receiving it twice daily, suggesting that valsartan is not being prescribed in line with its licence for many patients.

Prescribing data obtained from the GMS database suggest that ARB prescribing may not be optimal for maximum therapeutic benefit in hypertension and heart failure.

5. Summary

Preferred ARB: CANDESARTAN

- ✓ Candesartan is licensed for the treatment of hypertension and heart failure. It is administered once daily for both indications.
- ✓ For hypertension, candesartan is comparable to and possibly more effective than losartan. There is no head-to-head RCT comparing the BP-lowering effects of candesartan and valsartan but meta-analyses suggest they have similar efficacy.
- ✓ Candesartan significantly reduced cardiovascular death and hospital admissions for heart failure compared to placebo in a large prospective RCT of patients with CHF unable to tolerate an ACE inhibitor.
- ✓ Candesartan is recommended as an ARB for the treatment of hypertension and heart failure in a number of international clinical guidelines.
- ✓ Candesartan has a comparable or favourable cost profile relative to other ARBs.
- ✓ There are no significant differences between ARBs in terms of adverse effect profiles.
- ✓ Prescribing data obtained from the GMS database suggests that many ARBs are not optimally prescribed. The selection of once daily candesartan as the preferred ARB for hypertension and heart failure may enhance the quality of ARB prescribing nationally.

6. References

1. Health Products Regulatory Authority (HPRA) – Human Medicines Listings. Accessed at www.hrpra.ie on 7th July 2014.
2. National Centre for Pharmacoeconomics. Personal communication. On file.
3. General Medical Services (GMS) database. Data: January 2013 - March 2013. On file.
4. Edarbi® (azilsartan) SmPC. Last revised May 2014. Accessed at www.ema.europa.eu on 7th July 2014.
5. Atacand® (candesartan) 8 mg SmPC. Last revised December 2013. Accessed at www.hpra.ie on 7th July 2014. .
6. Teveten® (eprosartan) 400 mg SmPC. Last revised January 2014. Accessed at www.hpra.ie on 7th July 2014.
7. Aprovel® (irbesartan) 150 mg tablets SmPC. Last revised October 2013. Accessed at www.hpra.ie on 7th July 2014.
8. Cozaar® 50 mg tablets SmPC. Last revised March 2013. Accessed at www.hpra.ie on 7th July 2013.
9. Omesar® (olmesartan) 20 mg SmPC. Last revised May 2013. Accessed at www.hpra.ie on 7th July 2014.
10. Micardis (telmisartan) 40 mg SmPC. Last revised December 2013. Accessed at www.hpra.ie on 7th July 2013.
11. Diovan® (valsartan) 80 mg tablets SmPC. Last revised April 2014. Accessed at www.medicines.ie on 7th July 2014.
12. White WB *et al.* Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension 2011; 57 (3); 413-20.
13. Sica D *et al.* Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. Journal of Clinical Hypertension 2011; 13 (7); 467-72.
14. Riegger GAJ *et al* on behalf of the STRETCH Investigators. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexitil. *Circulation.* 1999; 100: 2224-2230.

15. Granger CB *et al* on behalf of the SPICE Investigators. Randomised trial of candesartan cilexitil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. *American Heart Journal* 2000; 139: 609-17.
16. Pfeffer MA *et al* on behalf of the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003 362: 759–66.
17. Granger CB *et al* on behalf of the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; 362: 772–776.
18. McMurray J *et al* on behalf of the CHARM investigators. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function treated with an ACE inhibitor: the CHARM-Added trial. *Lancet* 2003; 362**:** 767–71.
19. Lithell H *et al* on behalf of the SCOPE Investigators. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of Hypertension* 2003; 21(5):875-886.
20. Gradman AH et al on behalf of the Eprosartan Study Group. Assessment of Once-Daily Eprosartan, an Angiotensin II Antagonist, in Patients with Systemic Hypertension. *Clinical Therapeutics* 1999; 21(3): 442-453.
21. Murdoch D *et al*. ADEPT: Addition of the AT1 receptor antagonist eprosartan to ACE inhibitor therapy in chronic heart failure trial: hemodynamic and neurohormonal effects. *American Heart Journal* 2001; 141(5):800-807.
22. Lewis EJ et al on behalf of the Collaborative Study Group. Reboprotective effect of the angiotensin-II receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New England journal of Medicine* 2001;345(12): 851-860.
23. Pitt B *et al* on behalf of the ELITE Study Investigators. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; 349: 747–52.
24. Pitt B *et al* on behalf of the ELITE Study Investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure:

randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; 355: 1582–87.

25. Kjeldsen SE et al on behalf of the LIFE Study Group. Lowering of Blood Pressure and Predictors of Response in Patients With Left Ventricular Hypertrophy: The LIFE Study. *American Journal of Hypertension* 2000; 13:899–906.
26. Dahlof B et al on behalf of the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995–1003.
27. Brenner BM et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine* 2001; 345(12):861-9.
28. Dickstein K et al. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; 360:752–60.
29. Konstam MA et al on behalf of the HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; 374:1840–1848.
30. Oparil S et al. Comparative Efficacy of Olmesartan, Losartan, Valsartan, and Irbesartan in the Control of Essential Hypertension. *Journal of Clinical Hypertension* 2001; 3(5): 283-91.
31. Stumpe KO *et al*. Antihypertensive efficacy of Olmesartan compared with other antihypertensive drugs. *Journal of Human Hypertension* 2002; 16 (Suppl 2): S24-S28.
32. Brunner HR et al. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil assessed by 24-hour ambulatory blood pressure monitoring in patients with essential hypertension. *Clinical Drug Investigations* 2003; 23(7):419-430.
33. Malacco E *et al* on behalf of the ESPORT Study Group. Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild to moderate essential hypertension: the ESPORT trial. Journal of Hypertension 2010; 28: 2342-50.

34. Yusuf S *et al* on behalf of the TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; 372: 1174–83.
35. Yusuf S *et al* on behalf of the ONTARGET Investigators. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *New England Journal of Medicine* 2008; 358:1547-59.
36. Cohn J *et al* on behalf of the Valsartan Heart Failure Trial Investigators. A randomised trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *New England Journal of Medicine* 2001; 345 (23): 1667-1675.
37. Willenheimer R *et al* on behalf of the HEAVEN study group. Safety and efficacy of valsartan versus enalapril in heart failure patients. International Journal of Cardiology 2002; 85: 261-270.
38. Pfeffer MA *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *New England Journal of Medicine* 2003; 349: 1893-906.
39. Julius S *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan and amlodipine: the VALUE randomised trial. Lancet 2004; 363 (9426): 2022-2031.
40. Sega R. Efficacy and safety of eprosartan in severe hypertension. *Blood Pressure* 1999; 8:114-121.
41. McMurray JV, Swedberg K. HEALL: The final chapter in the story of angiotensin receptor blockers in heart failure – lessons learned from a decade of trials. *European Journal of Heart Failure*; 2010; 12(2): 99–103.
42. Makani H *et al*. Antihypertensive efficacy of angiotensin receptor blockers as monotherapy as evaluated by ambulatory blood pressure monitoring: a meta-analysis. *European Heart Journal.* First published online August 21, 2013. doi:10.1093/eurheartj/eht333 .
43. Heran BS, Wong MMY, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD003822.

44. Hudson M, Humphries K, Tu JV, Behlouli H, Pilote L. Angiotensin II receptor blockers for the treatment of heart failure – a class effect? *Pharmacotherapy* 2007; 27(4):526-534.
45. Desai et al. Comparative effectiveness of individual angiotensin receptor blockers on risk of mortality in patients with chronic heart failure. *Pharmacoepidemiology and Drug Safety* 2012; 21(3): 233–240.
46. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art. No.: CD003040.
47. Russell D *et al.* Cardiovascular Events in Subgroups of Patients during Primary Treatment of Hypertension with Candesartan or Losartan. *Journal of Clinical Hypertension* 2011;13(3):189-197.
48. Eklind-Cervenka M *et al.* Association of candesartan vs losartan with all-cause mortality in patients with heart failure. *JAMA* 2011;305(2):175-182.
49. Vidt VG *et al.* A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM-II. *Journal of Human Hypertension* 2001;15:475-480.
50. Zheng Z et al. A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension. *Journal of the Renin-Angiotensin-Aldosterone System* 2001; 12(3):365-374.
51. Hedner T *et al.* A comparison of the angiotensin-II antagonists valsartan and losartan in the treatment of essential hypertension. *American Journal of Hypertension* 1999; 12:414-417.
52. Fogari R et al. Comparative efficacy of losartan and valsartan in mild-to-moderate hypertension: results of 24-hour ambulatory blood pressure monitoring. *Current Therapeutic Research* 1999; 60(4):195-206.
53. Nixon RM, Muller E, Lowy A, Falvey H. Valsartan vs. other angiotensin II receptor blockers in the treatment of hypertension: a meta-analytical approach. *International Journal of Clinical Practice* 2009:63(5):766–775.

54. Ozaki N *et al.* Comparison of the effects of three angiotensin II receptor type 1 blockers on metabolic parameters in hypertensive patients with type 2 diabetes mellitus. *European Journal of Internal Medicine* 2010 (21):236-239.
55. McMurray *et al* on behalf of the Heart Failure Task Force of the ESC. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *European Heart Journal* 2012; 33: 1787–1847.
56. McMurray J *et al.* Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: Putting guidelines into practice. *European Journal of Heart Failure* 2005;7: 710 – 721.
57. National Institute for Health and Care Excellence. Clinical Guideline 108: Heart failure (2010).). Accessed at www.nice.org.uk on 15th July 2013.
58. American College of Cardiology Foundation/American Heart Association in collaboration with the International Society for Heart and Lung Transplantation. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. *Circulation* 2009;119:1977-2016.
59. Task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC Guidelines for the management of arterial hypertension. *European Heart Journal* doi:10.1093/eurheartj/eht151.
60. National Institute for Health and Care Excellence. Clinical Guideline 127: Hypertension (November 2011). Accessed at www.nice.org.uk on 15th July 2013.
61. Williams B *et al*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. *Journal of Human Hypertension* 2004; 18: 139–185.
62. National Institute for Health and Care Excellence - Clinical Knowledge Summaries (CKS). Clinical topic: Chronic Heart Failure (2010). Accessed at http://cks.nice.org.uk on 15th July 2013.
63. National Institute for Health and Care Excellence - Clinical Knowledge Summaries (CKS). Clinical topic: Hypertension [not diabetic] (2012). Accessed at http://cks.nice.org.uk on 15th July 2013

64. Brown MJ. General Cardiology - a rational basis for selection among drugs of the same class. *Heart* 2003; 89: 687–694.
65. HSE Primary Care Reimbursement Service (PCRS). Reimbursable items list. Accessed at www.pcrs.ie on 7th July 2014.
66. World Health Organisation (WHO) Collaborating Centre for Drugs Statistics Methodology. ATC/DDD Index 2014. Accessed at www.whocc.no on 7th July 2014.
67. British National Formulary (BNF) June 2014. Accessed at www.medicinescomplete.com on 7th July 2014.
68. Svanstrom H, Pasternack B, Hviid A. Association of treatment with losartan vs. candesartan on mortality among patients with heart failure. *JAMA* 2012; 307(14):1506-1512.

7. Bibliography

1. A. Menarini. Communication received 8th August 2013. On file.
2. AstraZeneca. Communication received 2nd August 2013. On file.
3. Bakris GL *et al*. The comparative effects of axilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. Journal of Clinical Hypertension 2011; 13: 81-88.
4. Bangalore S et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *American Journal of Medicine* 2007; 120:713-719.
5. Barrios V *et al*. Blood pressure goal achievement with olmesartan medoxomil-based treatment: additional analysis of the OLMEBEST study. *Vascular Health and Risk Management* 2009; 5:723-729.
6. Berry C, Norrie J, McMurray JJ. Are angiotensin II receptor blockers more efficacious than placebo in heart failure? Implications of ELITE-2. Evaluation of losartan in the elderly. *American Journal of Cardiology* 2001; 87:606–607.
7. Bonner G *et al*. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. Journal f Human Hypertension 2013; 27(8): 479-86
8. Brunner HR and Arakawa K. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil in achieving 24-hour blood pressure reductions and ambulatort blood pressure goals. *Clinical Drug Investigation* 2006; 26(4):185-193.
9. Chrysant SG, Marbury TC and Robinson TD. Antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-moderate hypertension. *Journal of Human Hypertension* 2003; 17:425-432.
10. Chrysant SG et al. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. *American Journal of Hypertension* 2004; 17:252-259.
11. Chrysant SG et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomised, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clinical Therapeutics* 2008; 30(4):587-604.

12. Conlin PR *et al.* Angiotensin II Antagonists for Hypertension: Are There Differences in Efficacy? *American Journal of Hypertension* 2000; 13(4): 418-426.
13. Daiichi Sankyo. Communication (undated); received August 2013. On file.
14. Fabia MJ *et al*. Antihypertesnive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24-hour ambulatory blood pressure monitoring, Journal of Hypertension 2007; 25:1327-1336.
15. Heuer HJ *et al*. Twenty-four hour blood pressure profile of different doses of candesartan cilexetil in patients with mild to moderate hypertension. *Journal of Human Hypertension* 1997; 11 (Suppl 2):S55-56.
16. Ichikawa S and Takayama Y. Long-term effects of olmesartan, and angiotensin-II receptor antaugonist, on blood pressure and the rennin-angiotensin-aldosterone system in hypertensive patients. *Hypertension Research* 2001; 24(6):641-646.
17. London New Drugs Group. APC/DTC Briefing Document, January 2008: ACE Inhibitors and Angiotensin II Receptor Antagonists for Hypertension. Accessed at www.evidence.nhs.uk (August 2013).
18. Mancia G *et al.* Reappraisal of European guidelines on hypertension management: a European society of Hypertension Task Force Document. *Journal of Hypertension* 2009;27: 2121-2158.
19. Mancia G *et al.* Heterogeneity in antihypertensive treatment discontinuation between drugs belonging to the same class. *Journal of Hypertension* 2011; 29: 1012-1018.
20. Menarini Pharmaceuticals Ireland Ltd. Correspondence received 9th August 2013. On file.
21. Meredith PA, Murray LS and McInnes GT. Comparison of the efficacy of candesartan and losartan: a meta-analysis of trails in the treatment of hypertension. *Journal of Human Hypertension* 2010; 24: 525-531.
22. MSD. Communication received 9th August 2013. On file.
23. Novartis Ireland Limited. Communication received 13th August 2013. On file.
24. Omboni S et al. Twenty-four hour and early morning blood pressure control of olmesartan vs. ramipril in elderly hypertensive patients: pooled individual data

analysis of two randomised, double-blind, parallel-group studies. *Journal of Hypertension* 2012;30: 1468-1477.

25. Puchler K, Laeis P and Stumpe KO. Blood pressure response but not adverse event incidence, correlates with dose of angiotensin-II antagonist. *Journal of Hypertension* 2001; 19: S1: S41-S48.
26. Savarese G *et al*. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *Journal of the American College of Cardiology* 2013; 61(2): 131-142.
27. Takeda. Communication received 8th august 2013. On file.
28. Smith D, Dubeil R and Jones M. Use of 24-Hour Ambulatory Blood Pressure Monitoring to assess Antihypertensive Efficacy: A comparison of Olmesartan Medoxomil, Losartan Potassium, Valsartan and Irbesartan. *American Journal of Cardiovascular Drugs* 2005; 5(1):41-50.
29. World Health Organisation (WHO/International Society of Hypertension (ISH) statement on management of hypertension. *Journal of Hypertension* 2003;21:1983-1992

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MEDICINES MANAGEMENT PROGRAMME

Appendix

Prescribing Tips for Candesartan

There is a range of candesartan preparations available. An up-to-date listing is available on the Health Products Regulatory Authority website at www.hpra.ie.

Therapeutic Indications

- Treatment of essential hypertension in adults.
- Treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤40%) as add-on therapy to ACE inhibitors or when ACE inhibitors are not tolerated.

Dosing and Administration

Full prescribing information is available in the Summary of Product Characteristics (SmPC) which may be accessed freely online at www.medicines.ie or www.hpra.ie.

Please consult the SmPC for guidance on prescribing in special patient populations, e.g. renal or hepatic impairment.

Table A1. Candesartan dosing and administration

Indication	Initial Dose	Titration & Maintenance	Comment
Hypertension	8 mg once daily	Increase the dose to 16 mg and further to 32 mg according to BP response.	Most of the antihypertensive effect is attained within 4 weeks.
Heart failure	4 mg once daily	Double the dose at intervals of at least 2 weeks to target dose of 32 mg	

DOSE Prescribe the correct dose and frequency for the patient's condition – see SmPC for details.

- ✓ **Hypertension**: start with 8 mg once daily
- ✓ **Heart failure:** start with 4 mg once daily
- ✓ **Up-titrate** by doubling the dose at intervals of at least two weeks

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

- In heart failure, the target dose of candesartan is 32 mg daily (or the nearest tolerated dose).

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.[62]
- ✓ **BP** – ARBs can cause hypotension, particularly in patients with heart failure and in hypertensive patients with intravascular volume depletion such as those receiving diuretics.

TARGET

- ✓ In most patients the **target SBP is <140 mmHg**. A **DBP target of <90 mmHg** is generally recommended, except in patients with **diabetes**, in whom values **<85 mmHg** are recommended.

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