ADIS DRUG EVALUATION

Clin Drug Investig 2012; 32 (9): 621-639
1173-2563/12/0009-0621/$49.95/0

Azilsartan Medoxomil

A Review of its Use in Hypertension

Caroline M. Perry

Adis, Auckland, New Zealand

Various sections of the manuscript reviewed by:

W.L. Baker, Schools of Pharmacy and Medicine, University of Connecticut, Farmington, Connecticut, USA; ***M. Burnier***, Division of Nephrology and Hypertension, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ***A. Coca***, Vascular Risk Prevention Unit, Hospital Clinico, University of Barcelona, Barcelona, Spain; ***L.M. Ruilope***, Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain.

Data Selection

Sources: Medical literature (including published and unpublished data) on 'azilsartan' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'azilsartan' or 'azilsartan medoxomil' and 'hypertension' or 'antihypertensive agent'. Searches were last updated 31 July 2012.

Selection: Studies in patients with hypertension who received azilsartan medoxomil. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Azilsartan, azilsartan medoxomil, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Abstract

Azilsartan medoxomil (Edarbi®; Ipreziv™) is an orally administered angiotensin II receptor type 1 antagonist (blocker) used in the treatment of adults with essential hypertension. This article reviews data on the clinical efficacy and

tolerability of azilsartan medoxomil in adults with essential hypertension and provides a summary of its pharmacological properties.

Azilsartan medoxomil is a prodrug that undergoes rapid hydrolysis in the gastrointestinal tract after oral administration to the bioactive moiety azilsartan, before systemic absorption. Azilsartan medoxomil produces antihypertensive effects by selectively blocking the binding of angiotensin II to the angiotensin type 1 (AT_1) receptor, thereby antagonizing the pressor response activity of angiotensin II.

In vitro, azilsartan produced greater and more sustained AT_1 receptor binding/blockade activity than several comparator angiotensin II receptor antagonists. Azilsartan medoxomil reduces blood pressure (BP) in hypertensive adults. In addition, the drug has been shown to have pleiotropic effects (i.e. effects beyond AT_1 receptor blockade).

In adults with essential hypertension, azilsartan medoxomil 20, 40 or 80 mg effectively reduced BP over a 24-hour period with once-daily administration in three major, randomized, controlled trials in which the primary endpoints were changes from baseline in 24-hour mean systolic BP (SBP) at week 6 (two trials) or week 24, assessed by ambulatory BP monitoring (ABPM). In the two 6-week trials, azilsartan medoxomil showed dose-dependent efficacy over all evaluated dosages and was more effective than placebo in lowering SBP. At the maximum approved dosage of 80 mg once daily, azilsartan medoxomil was significantly more effective than maximum dosages of olmesartan medoxomil (40 mg once daily) or valsartan (320 mg once daily), based on primary endpoint assessments. Mean reductions in clinic measurements of SBP and diastolic BP (DBP) measurements were also generally greater with azilsartan medoxomil 80 mg once daily than with the comparator drugs in these 6-week studies.

Over a longer treatment period of 24 weeks, azilsartan medoxomil showed sustained BP-lowering efficacy, with the reduction in 24-hour mean SBP at week 24 significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan 320 mg once daily. Mean reductions from baseline in mean clinic SBP and DBP as well as DBP by ABPM were also significantly greater with azilsartan medoxomil 40 or 80 mg once daily than with valsartan.

Azilsartan medoxomil was generally well tolerated, with a tolerability profile similar to that of placebo in the 6-week trials. Across the three major trials, headache and dizziness were among the most common adverse events. Overall, rates of treatment discontinuation as a result of adverse events were low in the 6-week and 24-week trials.

In conclusion, once-daily azilsartan medoxomil effectively lowers BP in adults with essential hypertension and has shown better antihypertensive efficacy than maximum therapeutic dosages of olmesartan medoxomil or valsartan in major trials of up to 24 weeks' duration. Azilsartan medoxomil is generally well tolerated and the low rates of discontinuation due to adverse events suggest that patients are likely to persist with long-term treatment. Azilsartan medoxomil is therefore a useful and attractive new option for lowering BP in patients with essential hypertension, particularly for those not able to tolerate other antihypertensive drugs. Further studies are required to evaluate the effects of azilsartan medoxomil on cardiovascular morbidity and mortality.

1. Introduction

Hypertension affects more than 25% of the adult population worldwide,[1] including more than 50% of people aged over 60 years in the UK,[2] and has been reported to have an age- and sex-adjusted prevalence of 44% in Europe.[3] The associated morbidity, mortality and huge costs to society make hypertension a major health problem worldwide.[2,4-8] Notably, hypertension is an important risk factor

for myocardial infarction, heart failure, haemorrhagic and ischaemic stroke, chronic renal disease, cognitive decline and premature death.[2,9,10] Across Europe, 22–25% of cases of myocardial infarction are the result of a history of high blood pressure (BP), and individuals with hypertension have slightly less than twice the risk of a myocardial infarction compared with those who do not have hypertension.[4]

In patients with hypertension, effective reduction of BP to accepted goals is required to reduce the risk of fatal or nonfatal cardiovascular events. The target BP advocated in current treatment guidelines is generally <140/90 mmHg, with a lower target (<130/80 mmHg) for patients with diabetes mellitus or heart or renal disease.[2,6,7,9]

Several classes of drugs are available for the treatment of patients with essential hypertension.[2,6,7,9] These include older drugs, such as diuretics, beta-adrenergic antagonists (blockers), alpha-adrenergic blockers and calcium channel blockers, and other drugs that affect the renin-angiotensin system (RAS), such as the direct renin inhibitors, the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II receptor antagonists (blockers), also known as ARBs.

Azilsartan medoxomil (Edarbi®; Ipreziv™) is a prodrug of azilsartan, a nonpeptide angiotensin II receptor type 1 (AT_1) antagonist, and has recently been approved in the EU[11] and the US for the treatment of patients aged ≥18 years with essential hypertension. In Japan, the drug is available as the active metabolite (azilsartan) that differs from the licensed compound in Europe and the US (azilsartan medoxomil), which is the prodrug formulation.[11] This article, written with a European focus, provides a review of data on the clinical profile of azilsartan medoxomil in adults with hypertension and includes a summary of its pharmacological properties. The chemical structure of azilsartan kamedoxomil, the potassium salt of azilsartan medoxomil, is shown in figure 1.

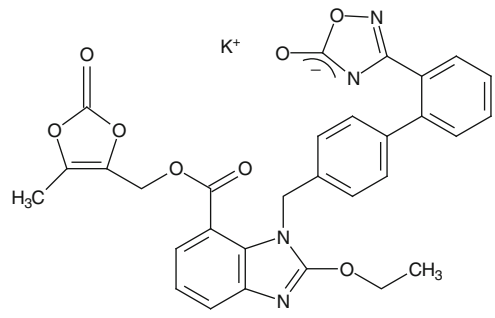

Fig. 1. Chemical structure of azilsartan kamedoxomil.

2. Pharmacodynamic Properties

Data on the pharmacodynamic properties of azilsartan medoxomil reviewed in this section are from several published studies,[12-16] the EU Summary of Product Characteristics (SPC)[11] and the European Public Assessment Report (EPAR).[17]

2.1 Mechanism of Action and Receptor Binding

Angiotensin II is the main pressor agent of the RAS. Its effects include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and the renal reabsorption of sodium, leading to water retention.[11] Azilsartan medoxomil is the prodrug of azilsartan (section 3). Azilsartan is an angiotensin II AT_1 receptor antagonist that exerts its antihypertensive effects by selectively blocking the binding of angiotensin II to the AT_1 receptor in multiple tissues, including the adrenal gland and vascular smooth muscle, thereby antagonizing the vasoconstrictor and aldosterone-secreting activity of angiotensin II and reducing BP. The mechanism of action of azilsartan is independent of the angiotensin II synthesis pathway.[11,17]

The affinity of azilsartan for the AT_1 receptor is >10 000-fold greater than that for the AT_2 receptor, which is also present in many human tissues but does not appear to play a role in cardiovascular homeostasis.[17] Although blockade of the angiotensin II receptor by azilsartan results in inhibition of the negative regulatory feedback of angiotensin II on renin secretion, the resultant increase in circulating levels of angiotensin II and plasma renin activity do not overcome the inhibitory effect of azilsartan on the pressor response to angiotensin II in patients with hypertension.[11]

Table I. *In vitro* binding affinities of azilsartan and other angiotensin II receptor antagonists[15]

Drug	IC_{50} nmol/L	IC_{50} nmol/L after a 5-h washout period
Azilsartan	2.6	7.4
Telmisartan	5.1	191.6
Olmesartan	6.7	242.5
Irbesartan	15.8	>10 000
Valsartan	44.9	>10 000

IC_{50} = 50% inhibitory concentration.

Azilsartan was more potent in terms of its AT_1 receptor blockade activity than several other angiotensin II receptor antagonist drugs in *in vitro* and *in vivo* investigations.[15,18] *In vitro*, binding of azilsartan to the AT_1 receptor occurred in a dose-dependent manner and the drug showed greater affinity for the AT_1 receptor (50% inhibitory concentrations [IC_{50}] 2.6 nmol/L), than the comparator angiotensin II receptor antagonists telmisartan, olmesartan, irbesartan and valsartan (table I).[15]

The inhibitory effects of azilsartan on the AT_1 receptor were maintained after a 5-hour washout period, indicating slow receptor dissociation, whereas a significant attenuation of the inhibitory effects of the four comparator drugs was observed, with IC_{50} values ranging from 191.6 to >10,000 nmol/L (table I).[15] Although the angiotensin II receptor antagonists share common structural characteristics that are prerequisite for effective antagonism of the angiotensin II receptor, structural differences in their side chains may affect the binding kinetics of these drugs. These structural differences may be, at least in part, responsible for variations in potency, time to dissociate from AT_1 receptors and durability of effect at the receptors (table I).[15]

2.2 Cardiovascular and Other Effects

Consistent with findings in earlier animal studies (reviewed by Volpe[19]), azilsartan medoxomil produces antihypertensive effects in adults with essential hypertension and reduced SBP to a clinically relevant extent in clinical trials (section 4).[11,20-22] The BP-lowering efficacy of azilsartan medoxomil in 3672 patients with mild, moderate or severe hypertension has been evaluated in seven randomized, double-blind, controlled trials.[11,17] These studies also included active treatment arms (n = 1468) and placebo arms (n = 801). Three of these studies are fully published[20-22] and are the main focus of section 4 where they are discussed in detail.

As well as effects on BP in adults with hypertension, azilsartan medoxomil has shown beneficial effects on cellular mechanisms of cardiovascular disease and on insulin sensitivity in several animal studies and cellular experiments.[12-14,16,23]

In blood vessel walls, plasminogen activator inhibitor type-1 (PAI-1) protein expression can be increased by angiotensin II and this may result in the acceleration of atherosclerosis.[12] Furthermore, after myocardial infarction, PAI-1 over-expression in the heart may contribute to negative left ventricular modelling and heart failure. Inhibition of the AT_1 receptor may potentially blunt expression of the PAI-1 protein in the wall of the aorta, thereby reducing the risk of atherosclerosis by decreasing atherosclerotic plaque formation and the likelihood of plaque rupture, a significant cause of morbidity and mortality globally.[12] In a preclinical study, azilsartan medoxomil, administered orally for 16 weeks, suppressed vascular wall expression of PAI-1 protein in over-expressing PAI-1 vascular smooth muscle cells in mice on a high-fat diet rendered PAI-1 over-expressors and prone to atherosclerosis. Across three dose regimens (0.1–10 mg/kg), the mice exposed to azilsartan had a decrease in aortic wall PAI-1 as well as increases in both the cellularity and collagen content of atherosclerotic plaques, consistent with the presence of more biologically stable plaques less likely to rupture.[12]

Some angiotensin II receptor antagonist drugs are known to be pleiotropic molecules and exhibit pharmacological effects beyond AT_1 receptor blockade-related effects that may be clinically relevant in terms of cardiovascular protection or in the treatment of conditions concomitant to cardiovascular disease.[13,14,18,23] Examples include the production of antiproliferative effects in vascular cells not stimulated with angiotensin II and without AT_1 receptors. In addition, several angiotensin II receptor antagonist drugs have been shown to have a direct effect at several types of peroxisome proliferator-activated receptors (PPARs) that are known to regulate various inflammatory and metabolic responses.[24-27] Although the BP-lowering effects and

mechanism of action of azilsartan as an AT_1 receptor antagonist are well known and its inhibitory effects on vascular contractility documented,[15] data are currently reasonably limited on its pleiotropic characteristics, such as its effects on vascular cell proliferation, adipogenesis and adipocyte gene expression (reviewed by Kajiya et al.[13]).

In an *in vitro* study that used cell-based assay systems, adipogenesis in cultured 3T3-L1 preadipocytes was enhanced by the presence of azilsartan, which also exerted more marked effects than valsartan on the expression of genes that encoded peroxisome proliferator-activated receptor-α (PPAR-α) PPAR-δ, adipsin, adiponectin and leptin.[13] Furthermore, in the absence of exogenously supplemented angiotensin II, azilsartan produced potent inhibition of vascular cell proliferation. At low concentrations (≥1 μmol/L), azilsartan inhibited the proliferation of aortic endothelial cells, whereas antiproliferative effects were not observed or were minimal with valsartan at concentrations <10 μmol/L. Azilsartan also displayed antiproliferative effects in cells without AT_1 receptors and, in vascular smooth muscle cells, blocked the activation of mitogen-activated protein kinase induced by angiotensin II; the latter effect was not observed with valsartan.[13]

Azilsartan medoxomil improved insulin sensitivity in hypertensive rats and also showed insulin-sensitizing effects in obese Koletsky rats.[14,16] The observed effects were independent of reductions in food intake, increased body weight, or of activation of the adipose PPAR-γ receptor that regulates adipogenesis.[14]

3. Pharmacokinetic Properties

Most of the data reviewed in this section on the pharmacokinetic properties of azilsartan medoxomil are derived from the EU SPC[11] and the EPAR,[17] with additional preliminary data from abstracts.[28,29]

Azilsartan medoxomil is hydrolysed in the gastrointestinal tract to azilsartan, the bioactive moiety, before systemic absorption. Results of *in vitro* investigations have shown that carboxymethylenebutenolidase is involved in the hydrolysis of azilsartan medoxomil in the intestine and liver; plasma esterases also play a role in the hydrolysis of azilsartan medoxomil to azilsartan.[11] Azilsartan medoxomil is undetectable in the plasma after oral administration of the drug.[17]

Maximum plasma concentrations of azilsartan are achieved within 1.5–3 hours after oral administration of azilsartan medoxomil.[11] After single or multiple doses ranging from 20 mg to 320 mg, dose proportionality in azilsartan systemic exposure was demonstrated.[17] Based on plasma concentrations of azilsartan, the estimated absolute oral bioavailability of azilsartan after administration of azilsartan medoxomil is ≈60%; the bioavailability of the drug is not affected by food.[11] Steady-state plasma concentrations of azilsartan are attained in 4–7 days and there is no evidence of accumulation of the drug after multiple-dose administration.[17]

Azilsartan has a volume of distribution of ≈16 L and is highly bound (>99%) to plasma proteins (predominantly albumin).[11] The extent of azilsartan protein binding is constant, even at plasma concentrations that are well above the therapeutic concentrations achieved with recommended doses.[11] Azilsartan-associated radioactivity was shown to cross the blood-brain barrier and also passed across the placental barrier in rats.[17]

Azilsartan undergoes metabolism to two primary metabolites that do not contribute to the pharmacological activity of azilsartan. Cytochrome P450 (CYP) 2C9 is the major enzyme responsible for the metabolism of azilsartan. The major metabolite (known as metabolite M-II) in plasma is formed by *O*-dealkylation; the minor metabolite (metabolite M-I) is formed by decarboxylation.[11] Systemic exposures to the major and minor metabolites were, respectively, ≈50% and <1% of azilsartan.[11]

After administration of an oral dose of ^{14}C-labelled azilsartan medoxomil, ≈55% of the radioactivity was recovered in the faeces and ≈42% was recovered in the urine, with 15% of the dose excreted as azilsartan in the urine. Renal clearance of azilsartan is approximately 2.3 mL/min and its elimination half-life is ≈11 hours.[11]

The presence of mild or moderate hepatic impairment (Child-Pugh classification) did not appreciably affect the pharmacokinetics of azilsartan after administration of single 40 mg doses of azilsartan medoxomil or multiple doses of 40 mg once daily (days 4–8 of administration), in a single-centre,

phase I study.[28] Similarly, the pharmacokinetics of azilsartan after administration of azilsartan medoxomil as single or multiple 60 mg doses (days 4–8) were not affected by sex, race or age in healthy volunteers.[29]

Azilsartan total exposure increased by 30%, 25% and 95%, respectively, in patients with mild, moderate and severe renal impairment[11] and no increase in exposure (+5%) was observed in patients with end-stage renal disease undergoing dialysis. Hemodialysis does not remove azilsartan from the systemic circulation.[11]

An extensive drug-drug interaction programme was completed for azilsartan medoxomil including studies with CYP substrates and inhibitors, P-glycoprotein substrates, and an organic cation transporter substrate. Interactions between azilsartan medoxomil and other drugs, mediated via inhibition of esterases, are unlikely, based on the results of *in vitro* studies. No clinically significant drug interactions have been observed in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone and warfarin.[11,17]

4. Therapeutic Efficacy

The therapeutic efficacy of oral azilsartan medoxomil in terms of its BP-lowering effects has been evaluated in three fully published trials in adults with essential hypertension.[20-22] Patients were naive to previous treatment with azilsartan medoxomil in all three studies. Four other randomized trials of azilsartan medoxomil have also been conducted in similar patient populations (section 2.2)[11] but have yet to be published and are not reviewed in this article. The three published trials were phase III, randomized, double-blind, multicentre, active comparator trials; two of the trials had an active treatment period of 6 weeks and also had a placebo control group,[20,21] and the third trial was a longer term trial, with no placebo arm, and had an active treatment period of 24 weeks.[22] Active comparators were other angiotensin II receptor antagonists in all three trials. Preliminary data, reported in an abstract, are also available regarding a randomized study comparing azilsartan medoxomil with ramipril.[30] The BP-lowering efficacy of azilsartan medoxomil administered as a single agent or in combination with other antihypertensive drugs has also been evaluated in studies reported in several other studies (section 4.3).

In the 6-week placebo-controlled trials, the BP-lowering efficacy of azilsartan medoxomil was compared with olmesartan medoxomil[20,21] and valsartan.[21] The 24-week trial compared the efficacy of azilsartan medoxomil with that of valsartan.[22] Inclusion and exclusion criteria, primary endpoints and other endpoints in these three major trials are summarized in table II. In the three trials,[20-22] the BP-lowering efficacy of azilsartan medoxomil was assessed by use of both ABPM and BP measurements obtained in the clinic (table II). Before randomization, all selected patients received placebo for a period of 2 weeks. This coincided with a washout period of 3–4 weeks for patients who had been previously treated with other antihypertensive drugs, to ensure a drug-free baseline for all patients.[20-22]

4.1 Short-Term Placebo-Controlled and Active Comparator Trials

4.1.1 Comparison with Olmesartan Medoxomil

The antihypertensive efficacy of azilsartan medoxomil at dosages up to the maximum of 80 mg once daily was compared with that of olmesartan medoxomil, at its maximum approved dosage (40 mg), or placebo in adults with primary hypertension in the trial reported by Bakris et al.[20] All patients were randomized to receive study treatment with azilsartan medoxomil 20 mg (n = 283), 40 mg (n = 283) or 80 mg once daily (n = 285), olmesartan medoxomil 40 mg once daily (n = 282) or placebo (n = 142) in a double-blind manner, with stratification by race (Black or non-Black). As well as the primary and secondary outcome analyses, subgroup analyses were performed by race, age <65 or ≥65 years, sex, 24-hour mean SBP at baseline, body mass index (BMI) and renal function.

In addition to a step-wise testing procedure with superiority testing for comparisons between azilsartan medoxomil and olmesartan medoxomil, the study had ≥90% power to demonstrate nonferiority between azilsartan medoxomil and olmesartan

Table II. Summary of inclusion and exclusion criteria, and efficacy endpoints in three randomized, double-blind, multicentre trials comparing oral azilsartan medoxomil monotherapy with other oral angiotensin II receptor antagonists or placebo in men and women aged ≥18 y with essential hypertension.[20-22] The primary endpoint was the change from baseline in 24-h mean systolic blood pressure at wk 6[20,21] or 24[22] assessed by ambulatory blood pressure monitoring

Main inclusion criteria	Main exclusion criteria	Secondary and other endpoints
Comparison with OLM or PL[20]		
Diagnosis of primary hypertension, defined as sitting trough clinic SBP ≥150 mmHg and ≤180 mmHg, and 24-h mean SBP ≥130 mmHg and ≤170 mmHg	Sitting DBP >114 mmHg; baseline ABPM of insufficient quality; history of major cardiovascular events; secondary hypertension; significant defects in cardiac conduction; severe renal impairment (estimated GFR <30 mL/min/1.73 m^2); suspected or known renal artery stenosis; poorly controlled type 2 diabetes mellitus, or type 1 diabetes; major hepatic abnormalities; hyperkalaemia; poor compliance during the initial placebo run-in period	Change from BL in 24-h mean DBP by ABPM; trough sitting clinic DBP; other SBP and DBP parameters by ABPM; proportion of treatment responders, defined as pts achieving a target clinic SBP of <140 mmHg and/or a reduction from BL in SBP of ≥20 mmHg
Comparison with OLM or VAL or PL[21]		
Diagnosis of hypertension, with a clinic SBP of ≥150 mmHg and ≤180 mmHg, and a 24-h mean SBP of ≥130 mmHg and ≤170 mmHg	Suspected or known secondary hypertension; severe diastolic hypertension (seated DBP >114 mmHg); clinically relevant or unstable cardiovascular disease; clinically significant renal impairment (estimated GFR: <30 mL/min/1.73 m^2) poorly controlled type II diabetes, or type 1 diabetes; hepatic, metabolic or psychiatric disorders	Change from BL in trough, seated, clinic SBP (main secondary endpoint); changes from BL in 24-h mean and clinic DBP measurements; proportion of treatment responders, defined as pts achieving a target clinic SBP of <140 mmHg and/or a reduction from BL in SBP of ≥20 mmHg
Comparison with VAL[22]		
Diagnosis of hypertension, with a clinic SBP of ≥150 mmHg and ≤180 mmHg and a 24-h mean SBP of ≥130 mmHg and ≤170 mmHg	Suspected or known secondary hypertension; severe diastolic hypertension (seated DBP >114 mmHg); recent history (<6 months) of major cardiovascular events; clinically significant renal dysfunction (estimated GFR <30 mL/min/1.73 m^2); poorly controlled type 2 diabetes, or type 1 diabetes; hyperkalaemia; poor compliance during the placebo run-in period	Change from BL in trough sitting clinic SBP; changes from BL in 24-hour mean DBP by ABPM and trough sitting clinic DBP; proportion of treatment responders defined as pts achieving a target clinic SBP <140 mmHg and/or a reduction from BL of ≥20 mmHg, clinic DBP <90 mmHg and/or a reduction of ≥10 mmHg from BL, or both

ABPM = ambulatory blood pressure monitoring; **BL** = baseline; **DBP** = diastolic blood pressure; **GFR** = glomerular filtration rate; **OLM** = olmesartan medoxomil; **PL** = placebo; **pts** = patients; **SBP** = systolic blood pressure; **VAL** = valsartan.

medoxomil for the primary endpoint. The non-inferiority margin was 1.5 mmHg.[20]

At baseline, there were no major between-group differences in patient characteristics, including baseline SBP and DBP. The mean 24-hour SBP was 146 mmHg at baseline. Approximately one-third (29.5%) of patients were aged ≥65 years and the mean age of the study population was 58 ± 11 years. The 6-week double-blind treatment period was completed by >90% of the randomized patients. Mild or moderate renal impairment was present in approximately half of the patients; 11.1% of the study population were Black and 72.8% were White.[20]

The main efficacy results reported at the end of the study (week 6) are presented in table III. Azilsartan medoxomil was effective in the treatment of hypertension, with dose-dependent reductions in 24-hour mean SBP (the primary endpoint) observed across the three azilsartan medoxomil treatment groups (table III). Recipients of azilsartan medoxomil 80 mg had a significantly greater reduction (by −2.1 mmHg; 95% CI −4.0, −0.1; p = 0.038) in 24-hour mean SBP, when assessed using the stepwise statistical analysis plan, than that attained in the olmesartan medoxomil treatment group (table III). Azilsartan medoxomil 40 mg was shown to be non-inferior to olmesartan medoxomil in terms of the

Table III. Antihypertensive efficacy of azilsartan medoxomil. Results of randomized, double-blind, multicentre trials comparing oral azilsartan medoxomil monotherapy with other oral angiotensin II receptor antagonists or placebo in adults with essential hypertension

Study (treatment duration; wk)	Treatment (mg once daily)	No. of evaluable pts[a]	Baseline 24-h mean SBP (mmHg)	Mean change from baseline in 24-h mean SBP, assessed by ABPM[b] (mmHg)	Response rate (% of pts)[c]
Comparison with OLM or PL					
Bakris et al.[20]	AZL-M 20	241	145.4	−12.2*	48
(6)	AZL-M 40	244	146.0	−13.5*[d]	50
	AZL-M 80	243	146.2	−14.6* †	57
	OLM 40	250	146.5	−12.6*[e]	53
	PL	120	146.3	−1.4	NR
Comparison with OLM or VAL or PL					
White et al.[21]	AZL-M 40	237	144.4	−13.4* ‡‡[d]	NR
(6)	AZL-M 80	229	144.6	−14.5* †† ‡‡	58‡
	VAL 320	234	146.3	−10.2*	49
	OLM 40	254	144.4	−12.0*	49
	PL	134	144.3	−0.3	22
Comparison with VAL					
Sica et al.[22]	AZL-M 40	284	146.0	−14.9‡‡	56‡
(24)	AZL-M 80	271	145.2	−15.3‡‡	59‡
	VAL 320	277	145.5	−11.3	47

a For the primary endpoint.

b Primary endpoint.

c See table II for definitions of response.

d Noninferior to OLM (noninferiority margin 1.5 mmHg).

e p-Value reported in drug company data on file.

ABPM = ambulatory blood pressure monitoring; **AZL-M** = azilsartan medoxomil; **NR** = not reported; **OLM** = olmesartan medoxomil; **PL** = placebo; **pts** = patients; **SBP** = systolic blood pressure; **VAL** = valsartan; * $p < 0.001$ vs PL; † $p = 0.038$ vs OLM; †† $p = 0.009$ vs OLM; ‡ $p \leq 0.05$ vs all comparator groups (excluding the AZL-M 40 mg group in the study reported by White et al.[21]); ‡‡ $p \leq 0.001$ vs VAL.

primary endpoint, with a treatment difference of −0.92 mmHg (95% CI −2.87, 1.02). Decreases in ambulatory measurements of SBP were observed throughout the 24-hour dosage interval.[20]

Similarly, dose-related absolute mean reductions in sitting trough clinic SBP values ranging from −14.3 to −17.6 mmHg occurred across the azilsartan medoxomil treatment groups, compared with a reduction in SBP of −14.9 mmHg in the olmesartan medoxomil group and −2.1 mmHg in the placebo group. Changes from baseline in clinic SBP by study visit are shown in figure 2 and indicate that the marked reductions in clinic SBP achieved in the active treatment groups had reached a plateau by week 4 and were sustained during the study.

For the three azilsartan medoxomil treatment groups, mean reductions in clinic SBP were significantly ($p < 0.001$) greater than in the placebo group. Comparisons between azilsartan medoxomil 20 and 40 mg showed nonsignificant differences in mean reductions in sitting trough clinic SBP, whereas the reduction in mean clinic SBP was significantly greater with azilsartan medoxomil 80 mg than with olmesartan medoxomil (by −2.7 mmHg; 95% CI −5.3, −0.1; $p = 0.043$). However, despite statistical signifance, superiority could not be claimed because the analysis was halted at a previous step. When adjusted for placebo, mean reductions in clinic SBP in the recipients of azilsartan medoxomil 20, 40 or 80 mg were −12.2, −12.4, and −15.5 mmHg versus −12.8 mmHg for olmesartan medoxomil.[20]

Mean reductions in both 24-hour mean DBP and clinic DBP were broadly similar to the reductions in SBP across all of the treatment groups.[20] Placebo-subtracted reductions from baseline in 24-hour mean DBP in the azilsartan medoxomil 20,

40 and 80 mg treatment groups were −6.8, −7.7 and −7.9 mmHg, versus −7.0 mmHg with olmesartan medoxomil. Corresponding mean reductions in clinic DBP were −7.0, −7.1 and −8.6 mmHg for azilsartan medoxomil and −7.1 mmHg for olmesartan medoxomil. The decrease in clinic DBP achieved in the azilsartan medoxomil 80 mg group was significantly greater than that achieved in the olmesartan medoxomil group; the treatment difference was −1.5 mmHg (95% CI −3.0, −0.04; p = 0.044). As shown in table III, treatment response rates of ≈50–60% were achieved across the three azilsartan medoxomil treatment groups and in 53% of the olmesartan medoxomil recipients. The efficacy of azilsartan medoxomil 80 mg, in terms of response rates, was not significantly different from that of olmesartan medoxomil 40 mg; the odds ratio for the comparison between the two groups was 1.15 (95% CI 0.83, 1.62; p = 0.402).[20]

Subgroup analyses showed that age, sex, baseline median 24-hour mean SBP and baseline estimated glomerular filtration rate had no appreciable influence on treatment efficacy.[20] As with all other angiotension II receptor antagonists and ACE inhibitors, azilsartan medoxomil may be less effective in lowering blood pressure in Black patients[11] and race did have an effect, with the Black patients experiencing less of an effect on 24-hour mean SBP than the non-Black patients.[20] In the subgroup of Black patients, the placebo-subtracted changes from baseline in 24-hour mean SBP in the azilsartan medoxomil 20, 40 and 80 mg groups were, respectively, −4, −5.2 and −5.1 mmHg, compared with −3 mmHg with olmesartan medoxomil 40 mg; the difference in SBP between the azilsartan medoxomil 80 mg and olmesartan medoxomil 40 mg groups, in favour of the azilsartan medoxomil 80 group, was −2.1 mmHg (95% CI −7.7, 3.5). BMI also appeared to affect treatment response. In patients with a BMI of ≥30 kg/m^2, the placebo-subtracted changes from baseline in 24-hour mean SBP in the azilsartan medoxomil 20, 40 and 80 mg groups were −9.8, −11.9 and −13.6 mmHg, respectively, compared with −10.9 mmHg in the olmesartan medoxomil group; the difference in SBP between the azilsartan medoxomil 80 mg and olmesartan 40 mg group, in favour of the azilsartan medoxomil 80 group, was −2.7 mmHg (95% CI −5.8, 0.32). In patients with a BMI of <30 kg/m^2, corresponding reductions in SBP in the azilsartan medoxomil groups were −11.4, −11.9 and −12.8 mmHg versus −11.1 mmHg with olmesartan medoxomil; the difference in SBP between the azilsartan medoxomil 80 mg and olmesartan medoxomil 40 mg group, in favour of the azilsartan medoxomil 80 mg group, was −1.7 mmHg (95% CI −4.2, 0.9).[20]

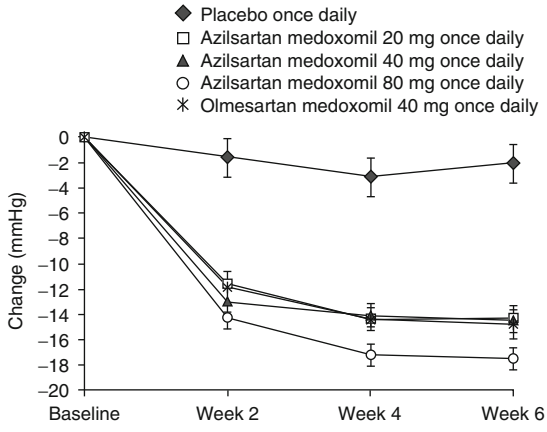

Fig. 2. Efficacy of oral azilsartan medoxomil (AZL-M) in adults with primary hypertension. Changes from baseline in clinic systolic blood pressure (SBP) by study visit in patients randomized to receive treatment with AZL-M 20 mg once daily (n = 283), AZL-M 40 mg once daily (n = 283), AZL-M 80 mg once daily (n = 285), olmesartan medoxomil 40 mg once daily (n = 282), or placebo (n = 142) for 6 weeks in a double-blind, multicentre trial.[20] Results are for all patients with baseline and post-baseline clinic SBP results, with the last observation carried forward. Reproduced and adapted from Bakris et al.[20] with permission from Wiley Periodicals, Inc.

4.1.2 Comparison with Olmesartan Medoxomil or Valsartan

The placebo-controlled study reported by White et al.[21] in patients with stage 1 or 2 hypertension evaluated the efficacy of 6 weeks' treatment with azilsartan medoxomil (40 or 80 mg once daily) with that of maximum approved dosages of olmesartan medoxomil (40 mg once daily) and valsartan (320 mg once daily). Primary and secondary endpoints in this trial are presented in table II. Patients meeting study inclusion criteria were randomly assigned to receive treatment with azilsartan medoxomil 20 or 40 mg once daily, olmesartan medoxomil 20 mg once daily, valsartan 160 mg once daily, or placebo for 2 weeks. Thereafter, for the

next 4 weeks, dosages of study drugs were force-titrated to azilsartan medoxomil 40 or 80 mg once daily, olmesartan 40 mg once daily or valsartan 320 mg once daily, or placebo was continued. Clinical assessments, including BP measurements, were conducted at baseline and every 2 weeks thereafter. All study drugs and placebo were administered in the morning. Step-wise hierarchical statistical analysis testing was performed to assess the superiority of azilsartan medoxomil over placebo. This was followed by a noninferiority analysis of primary and key secondary results and then statistical superiority testing of azilsartan medoxomil (80 mg then 40 mg) compared with the active comparators. The noninferiority margin was 1.5 mmHg. Subgroup analyses of primary and secondary endpoint results were also conducted (by age, race, sex and BMI).[21]

Of 3560 screened patients, 2661 were included in the placebo-run-in period and 1291 met enrolment criteria and were randomized to receive study treatment. The trial was completed by 1175 of the 1291 enrolled patients. At baseline, there were several statistically significant ($p \leq 0.03$), but not clinically relevant, differences in the 24-hour mean and daytime DBPs across the five treatment groups. The mean clinic SBP at baseline was 156–158 mmHg and the mean clinic DBP was 92–93 mmHg; the 24-hour mean SBP was 144–146 mmHg and the mean DBP was 88–90 mmHg. The mean age of the entire study group was 56 years (54% male) and the majority of patients were White (62%–67%). As shown in table III, patients in all active treatment groups had reductions from baseline in 24-hour mean SBP values at the study endpoint (week 6).[21]

Primary endpoint assessments showed that azilsartan medoxomil 80 mg once daily was significantly more effective than placebo and both valsartan 320 mg once daily and olmesartan 40 mg once daily (table III). Azilsartan medoxomil 40 mg once daily was significantly more effective than valsartan (mean difference vs valsartan was −3.2; [95% CI −5.1, −1.3; $p = 0.001$]) and noninferior to olmesartan medoxomil (mean difference vs olmesartan medoxomil was −1.4 [95% CI −3.3, 0.5]).[21]

Clinic SBP was also reduced from baseline in all of the active treatment groups, with mean clinic SBP values significantly ($p < 0.001$) lower than for placebo at 6 weeks. The greater antihypertensive efficacy of azilsartan medoxomil 80 mg was sustained throughout the study. Placebo-adjusted reductions in clinic SBP at week 6 were −14.6 and −14.9 mmHg for the azilsartan medoxomil 40 and 80 mg groups, respectively, and were −9.5 and −11.4 mmHg for the valsartan and olmesartan medoxomil groups. For assessments of clinic SBP, both dosages of azilsartan medoxomil were significantly more effective than both olmesartan medoxomil 40 mg ($p \leq 0.018$) and valsartan ($p < 0.001$).[21] Similar findings were reported for 24-hour and clinic DBP assessments, with reductions significantly ($p < 0.05$) greater in the azilsartan medoxomil 80 mg treatment group than in the valsartan and olmesartan medoxomil groups, and reductions in the azilsartan medoxomil 40 mg group greater than those achieved in the valsartan recipients.

Compared with recipients of placebo or once-daily valsartan 320 mg or olmesartan 40 mg, a significantly ($p = 0.05$) larger proportion of patients treated with azilsartan medoxomil 80 mg once daily (almost 60%) had a treatment response, i.e. a reduction of clinic SBP to <140 mmHg or a reduction of ≥20 mmHg (table III).

Analysis of results in the different subgroups showed that reductions from baseline in SBP (ambulatory measurements) were similar in men and women, and in obese patients and patients of normal weight. There were also no statistically significant differences in reductions from baseline in 24-hour mean SBP by age or by race.[21]

4.2 Long-Term Active Comparator Trial

The 24-week randomized study reported by Sica et al.[22] in adults with stage 1 or 2 hypertension evaluated the efficacy of azilsartan medoxomil at two approved (including the highest) dosages compared with that of valsartan at the highest approved dosage of 320 mg once daily (table III).

At screening, 702 (71.5%) of 982 patients were receiving antihypertensive drugs. At the start of the active treatment phase, patients eligible for randomization were assigned to receive azilsartan medoxomil 20 mg once daily force-titrated to 40 mg once daily after 2 weeks, or azilsartan medoxomil 20 mg once daily force-titrated to 80 mg once daily after 2 weeks, or valsartan 80 mg daily for 2 weeks

force-titrated to 320 mg daily after 2 weeks, with treatment continued at the higher dosages for 22 weeks (treatment duration 24 weeks in total). At randomization, patients were stratified by race (Black or non-Black). At each visit, trough sitting SBP and DBP were measured and ABPM was conducted for 24 hours on the day before randomization and prior to the first dose of double-blind study treatment, and thereafter at the end of week 8 and week 24. A step-wise hierarchical testing procedure was used to control the primary analysis, with noninferiority testing followed by superiority testing. For the primary endpoint, the noninferiority margin was 1.5 mmHg between azilsartan medoxomil and valsartan. Subgroup analyses were also conducted. Similar proportions of men and women were included and the mean age of all randomized patients was 58 years. The majority (≈76%) of patients were White and ≈15% were Black. At baseline, the 24-hour mean and clinic SBP and DBP values were, respectively, ≈145.6/87.9 mmHg and 157.2/91.2 mmHg.[22]

Changes from baseline in 24-hour mean SBP assessed by ABPM at week 24 (the primary endpoint) and other results are summarized in table III and in figure 3. Azilsartan medoxomil, at both dosages, and valsartan were shown to lower 24-hour mean SBP (table III). At week 24, reductions from baseline in 24-hour mean SBP were significantly ($p < 0.001$) greater in both the azilsartan medoxomil 40 and 80 mg treatment groups than with valsartan. Timewise efficacy effects after 24 weeks of treatment were also assessed for patients in each treatment group. Consistent with the primary endpoint results, both azilsartan medoxomil 40 and 80 mg reduced ambulatory SBP to a greater extent than did valsartan at the hourly assessments, with mean reductions from baseline generally smaller during the 16- to 24-hour period after drug administration than during the 1 to 15 hours after administration.

Reductions from baseline in clinic SBP measurements (similar across groups at baseline) were observed from 2 weeks after the start of treatment until week 24. At week 24, reductions from baseline in mean clinic SBP were significantly greater in the recipients of azilsartan medoxomil 40 mg (−14.9 mmHg; $p = 0.015$) or 80 mg (−16.9 mmHg; $p < 0.001$) once daily than in the patients treated with valsartan (−11.6 mmHg) [figure 3].[22]

Changes from baseline in ambulatory and clinic DBP measurements were consistent with the changes in SBP, with recipients of azilsartan medoxomil 40 or 80 mg generally having significantly greater changes from baseline than patients treated with valsartan. Relative to valsartan, mean reductions

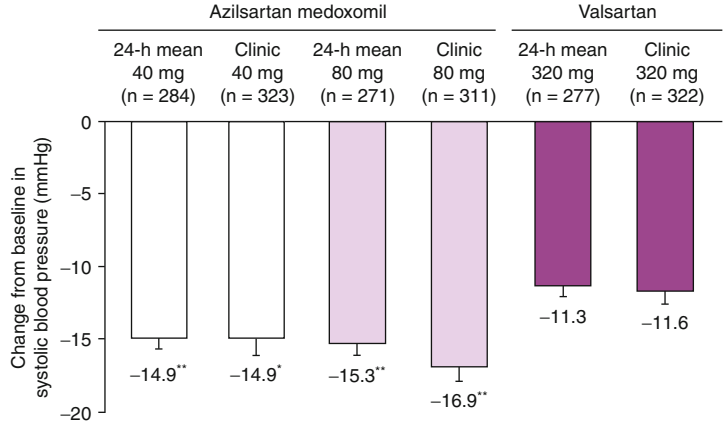

Fig. 3. Efficacy of oral azilsartan medoxomil (AZL-M) in adults with primary hypertension. Mean reductions from baseline in 24-hour mean systolic blood pressure (SBP), assessed by ambulatory blood pressure monitoring, and clinic SBP (in mmHg) in patients randomized to receive treatment with AZL-M 40 mg once daily (n = 327), AZL-M 80 mg once daily (n = 329) or valsartan (VAL) 320 mg once daily (n = 328) for 24 weeks in a double-blind, multicentre trial.[22] Reproduced and adapted from Sica et al.[22] with permission from Wiley Periodicals, Inc. * $p = 0.015$; ** $p < 0.001$ vs VAL.

from baseline in 24-hour DBP for patients in the azilsartan medoxomil 40 mg and 80 mg groups were −2.16 and −2.69, respectively ($p < 0.001$); corresponding reductions in clinic DBP were −2.52 and −2.76 ($p \leq 0.001$).[22]

Treatment response rates were also significantly higher in the patients who received azilsartan medoxomil 40 or 80 mg once daily ($p = 0.016$ and $p = 0.002$) than in the valsartan treatment group (table III). Similarly, results of the subgroup analyses based on age, race and sex showed that patients treated with either dosage of azilsartan medoxomil had a significantly greater decrease in 24-hour mean SBP than valsartan recipients; reductions in the two azilsartan medoxomil groups did not differ significantly based on age (<65 years or aged ≥65 years) or sex. Treatment effects observed in Black patients relative to non-Black patients were smaller ($p = 0.071$) in all of the treatment groups.[22]

4.3 Other Trials

Long-term treatment (24 weeks) with azilsartan medoxomil was more effective than ramipril in lowering BP in a randomized, double-blind trial of 884 adults with hypertension (baseline clinic SBP 150–180 mmHg).[30] After an initial treatment period of 2 weeks, when patients received azilsartan medoxomil 20 mg once daily or ramipril 2.5 mg once daily, patients were assigned once-daily treatment with azilsartan medoxomil 40 or 80 mg, or ramipril 10 mg. The primary endpoint was the change from baseline in trough sitting clinic systolic BP. Both dosages of azilsartan medoxomil were significantly ($p < 0.001$) more effective than ramipril on the primary endpoint; reductions from baseline in mean clinic SBP were −20.6 mmHg and −21.2 mmHg for the azilsartan medoxomil 40 and 80 mg groups, respectively, and −12.2 mmHg for the ramipril recipients. At both dosages, azilsartan medoxomil was also significantly more effective than ramipril in lowering 24-hour mean SBP. Furthermore, response rates were also significantly ($p < 0.001$) higher in the azilsartan medoxomil groups (≈54%) than with ramipril (33.8%).[30]

In other studies reported in abstracts or fully published papers, azilsartan medoxomil has shown efficacy as monotherapy[31,32] or in combination with chlorthalidone[33-35] or amlodipine[36] in the treatment of adults with hypertension.

Results of two monotherapy studies that used Monte Carlo simulation models suggested that azilsartan medoxomil was more effective than valsartan or olmesartan medoxomil (over 12 months) in achieving SBP goals in patients with uncontrolled essential hypertension without[32] or with diabetes mellitus.[31] The models included large hypothetical cohorts of patients from the National Health and Nutrition Examination Survey 1999–2006 and used data from the azilsartan medoxomil clinical trial programme, and a Healthcare Effectiveness Data and Information Set definition of controlled hypertension of <140/90[32] or <130/80 mmHg.[31] Based on the assumption of perfect treatment adherence, in patients without diabetes (mean age 53 years; 53% male) it was estimated that SBP goals would be achieved in 46% of azilsartan medoxomil, 34.4% of valsartan, and 41% of olmesartan recipients.[32] Corresponding results for the patients with diabetes in the other study (mean age 56 years; 56% male) were 41%, 26.8% and 28.8% for azilsartan medoxomil, valsartan and olmesartan medoxomil, respectively.[31] Once-daily azilsartan monotherapy was more effective than candesartan in a 16-week, randomized, double-blind study in 622 Japanese patients with grade I–II essential hypertension.[37] Of note, this study evaluated a different formulation of azilsartan (Azilva®) rather than azilsartan medoxomil (Edarbi®) and the doses of candesartan used reflect Japanese clinical practice.

The efficacy of a fixed-dose combination of azilsartan medoxomil/chorthalidone has been evaluated in two fully published studies.[34,35] These studies are not discussed further in this European-focused review as the fixed-dose formulation is not currently available in the EU.

Azilsartan medoxomil 40 or 80 mg in combination with chlorthalidone 25 mg, each administered once daily, was more effective than placebo in combination with chlorthalidone in 448 patients with stage II hypertension in a randomized, 6-week trial. The primary endpoint was the change from baseline in 24-hour mean SBP. Patients treated with azilsartan medoxomil 40 or 80 mg plus chlorthalidone had a significantly ($p < 0.001$) greater reduc-

tion in 24-hour mean SBP at week 6 (–31.7 and –31.3) than the recipients of placebo plus chlorthalidone (–15.9).[33]

Combination therapy with azilsartan medoxomil and amlodipine for 6 weeks was an effective treatment for patients with stage 2 hypertension (mean age 58 years; 51% male) in a randomized, double-blind, placebo-controlled study.[36] Reductions from baseline in 24-hour mean SBP by ABPM (the primary endpoint) were significantly ($p < 0.001$) greater in patients treated with azilsartan medoxomil 40 or 80 mg once daily plus amlodipine 5 mg once daily (–27 and –25.5 mmHg, respectively) than in recipients of placebo plus amlodipine (–15.9 mmHg).

5. Tolerability

Azilsartan medoxomil tolerability data reviewed in this section are largely derived from the three randomized, controlled trial reports reviewed in section 4,[20-22] the EU SPC[11] and the EPAR.[17] All data discussed relate to the clinical use of the drug in adults with essential hypertension.

Azilsartan medoxomil, at dosages of 20, 40 or 80 mg once daily, was generally well tolerated by adults with hypertension over a treatment period of up to 24 weeks in the three randomized controlled trials[20-22] (section 4; table III).

The tolerability profile of azilsartan medoxomil was similar to that of placebo in the two 6-week trials and the most common adverse events were headache and dizziness.[20,21]

In the trial that compared azilsartan medoxomil with olmesartan medoxomil or placebo,[20] the 6-week double-blind treatment period was completed by >90% of patients; adverse events, lack of efficacy and voluntary withdrawal were the most common reasons for treatment discontinuation. Of the 1272 randomized patients, 485 experienced at least one adverse event. The most common adverse events across all treatment groups (azilsartan medoxomil 20, 40 or 80 mg once daily, olmesartan medoxomil 40 mg or placebo) during the 6-week double-blind period were headache, dyslipidaemia and dizziness. The incidence of headache was 3.2–5.6% for azilsartan medoxomil 20–80 mg, 3.2% for olmesartan medoxomil and 7.0% for placebo; the corresponding incidence of dyslipidaemia was 3.5–5.6%, 3.5% and 2.1%, and for dizziness 2.1–2.8%, 3.5% and 2.8%. Rates of discontinuation due to adverse events and serious adverse events were higher (statistical analysis not reported) in the azilsartan medoxomil 20 mg (incidence 3.9% and 2.8%) and placebo (4.2% and 2.1%) groups than in the other treatment groups (≤2.1% and <1%). There was one death in the azilsartan medoxomil 20 mg group: the patient had a history of liver disease and was abusing alcohol.[20]

In the trial reported by White et al.[21] that compared azilsartan medoxomil with olmesartan medoxomil, valsartan or placebo, at least one dose of study drug was received by 1286 patients and 635 (49.4%) of these experienced at least one adverse event during the 6-week double-blind period. Treatment-emergent adverse events re-

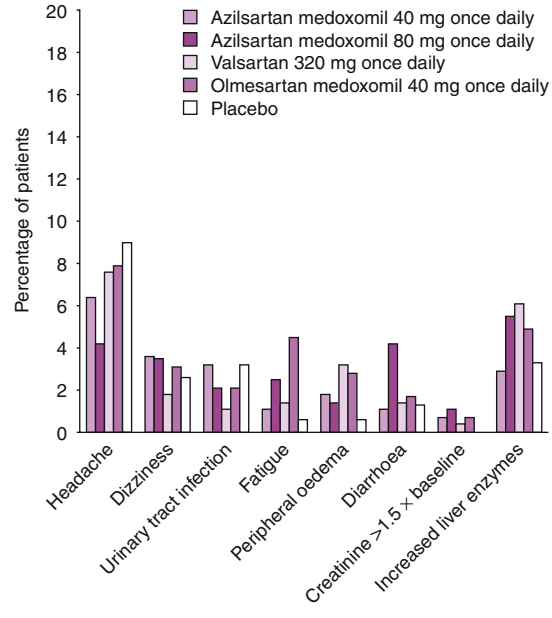

Fig. 4. Tolerability profile of azilsartan medoxomil compared with valsartan, olmesartan medoxomil and placebo in adults with essential hypertension. Treatment-emergent adverse events (incidence >3% in any treatment group) reported in adults in any treatment group in a randomized, double-blind, multicentre, placebo-controlled, 6-week study.[21] Hepatic enzymes were ALT, AST and gamma-glutamyl transpeptidase at levels 3 × the upper limit of normal.

ported in >3% of patients in any treatment group in this study are shown in figure 4. The most common adverse events reported were headache, dizziness and urinary tract infection (figure 4); these events were distributed reasonably evenly across all five treatment groups, as were the few reports of serious adverse events, which occurred in 14 patients overall. No deaths were reported during the study. An increase in serum creatinine of ≥50% above baseline was observed in ≤1.1% of patients. All increases in serum creatinine were reversible upon treatment discontinuation. There were no reports of elevated serum potassium levels of >6.0 mmol/L in any of the study participants.[21]

The tolerability profile of azilsartan medoxomil was similar to that of valsartan in the 24-week trial that compared azilsartan medoxomil 40 or 80 mg once daily with valsartan 320 mg once daily (the highest approved dosage).[22] Of the 984 patients randomized to treatment, 742 completed the study. The most common reasons for treatment discontinuation during the double-blind treatment phase were voluntary withdrawal (incidence 6.7%), adverse events (6.6%) and inadequate reduction in BP (5.1%). Treatment-emergent adverse events were usually mild to moderate in severity and rates of treatment discontinuation (as a result of adverse events) were low (≤8.2%) across the three treatment groups.[22] Treatment-emergent adverse events were reported in 65.4%, 65.3% and 59.2% of patients in the azilsartan medoxomil 40 mg, azilsartan medoxomil 80 mg and valsartan 320 mg groups, respectively, and the incidences of specific treatment-emergent adverse events were similar across the groups. Consistent with the tolerability findings of the 6-week trials,[20,21] the most common of these events in recipients of azilsartan medoxomil were headache and dizziness; urinary tract infection was also reported as a common adverse event.

Serious adverse events were reported in 2.4% and 1.5% of patients who received once-daily azilsartan medoxomil 40 and 80 mg, respectively, and in 2.5% of the valsartan recipients. There were two reports of sudden death: one in the azilsartan medoxomil 40 mg group and one in the valsartan group.[22] Small mean changes from baseline in serum creatinine, potassium and liver enzyme levels were observed in all of the treatment groups. Consecutive increases from baseline of ≥50% and above the upper limit of normal in serum creatinine levels were observed in two patients: one in each of the azilsartan medoxomil groups. Hyperkalaemia, defined as a serum potassium level of >6 mmol/L, was more common with azilsartan medoxomil 40 mg (1.8%) than with azilsartan medoxomil 80 mg (0.3%) or valsartan (0.6%).[22]

Adverse reactions reported in the EU SPC[11] were usually mild, not dose-related and did not differ by race, sex or age. The most common adverse reaction (incidence ≥1/100 to <1/10) was dizziness (classed as a nervous system disorder).[11] Diarrhoea was also reported as a common (incidence ≥1/100 to <1/10) adverse reaction. Clinically relevant changes in standard laboratory parameters were seldom reported in recipients of azilsartan medoxomil. In patients treated with azilsartan medoxomil 80 mg once daily, small reversible increases in serum creatinine were observed; increases in blood creatinine may be greater in patients receiving coadministered chlorthalidone,[11] consistent with other angiotensin II receptor antagonists and also ACE inhibitors.[11]

The incidence of peripheral oedema was increased from uncommon (≥1/1000 to <1/100) to common (≥1/100 to <1/10) when azilsartan medoxomil was administered in combination with amlodipine, but remained lower than that reported for amlodipine as a single agent. Small mean increases in serum uric acid levels were seen in recipients of azilsartan compared with placebo (10.8 μmol/L vs 4.3 μmol/L).[11] Prolongation of the corrected QT interval was not observed in healthy volunteers who received a single dose of azilsartan medoxomil 320 mg (i.e. a dose four times the highest maximum approved dose) in a double-blind, placebo-controlled and moxifloxacin-controlled study.[38]

6. Dosage and Administration

Azilsartan medoxomil, administered orally, is indicated for the treatment of adults with essential hypertension. The recommended starting dosage in the EU is 40 mg once daily, increased to a maximum of 80 mg once daily for patients who

do not achieve adequate BP with the lower dose. Azilsartan medoxomil may be taken with or without food.[11]

After 2 weeks of treatment, a near maximal antihypertensive effect is expected; maximal antihypertensive effects are achieved after 4 weeks of treatment with the drug.[11] For patients with inadequate control of BP after treatment with azilsartan medoxomil, additional reduction of BP may be achieved by co-administration with other antihypertensive agents, including diuretics (e.g. chlorthalidone and hydrochlorothiazide) and calcium channel blockers.[11]

As there is no clinical experience of the use of azilsartan medoxomil in the treatment of hypertensive patients with severe renal impairment and end-stage renal disease, caution is advised regarding the use of the drug in these patients.[11] Dosage adjustment of azilsartan medoxomil is not required for patients with mild or moderate renal impairment. Azilsartan is not removed from the systemic circulation by haemodialysis.[11] In the EU, close monitoring of patients with mild to moderate hepatic impairment receiving azilsartan medoxomil is recommended and a starting dose of 20 mg should be considered.[11] Azilsartan medoxomil has not been evaluated in patients with severe hepatic impairment and so dosage recommendations are not available for this patient group.[11]

Initial dose adjustment is not required for elderly patients, although a starting dose of 20 mg may be considered for very elderly (aged ≥75 years) patients who may be at risk of hypotension.[11]

Although epidemiological evidence of the risk of teratogenicity with angiotensin II receptor antagonists is currently limited and inconclusive, drugs in this class are not recommended for use during pregnancy.[11] Data are as yet unavailable on the use of azilsartan medoxomil in pregnant women, but studies have shown reproductive toxicity in animals exposed to the drug. Treatment with azilsartan medoxomil should be discontinued immediately and alternative treatment prescribed when pregnancy is detected.[11] Close observation for hypotension should be performed for infants of mothers who have taken angiotensin II receptor antagonists during pregnancy.[11]

Local prescribing information should be consulted for contraindications, special warnings and precautions for use.

7. Place of Azilsartan Medoxomil in the Management of Hypertension

Hypertension is an important yet preventable cause of morbidity and mortality.[1,2,4-9,39] Individuals with hypertension not receiving appropriate treatment often have a progressive increase in BP and this can result in vascular and renal damage, leading to a treatment-resistant state. Importantly, for each 2 mmHg increase in SBP, there is a 7% increase in the mortality risk associated with ischaemic heart disease and a 10% increase in the risk of death from a stroke.[2] Therefore, prompt initiation of appropriate therapy is crucial for those affected in order to avoid the development of progressive disease and reduce the risk of mortality. Although major advances have been made in the treatment of hypertension, it remains inadequately managed.[10]

Numerous guidelines for the effective management of hypertension have been published. To be useful and relevant to clinical practice, treatment guidelines should be up-to-date and based on best available evidence.[2] Current major treatment guidelines recommend a reduction in BP to <140/90 mmHg and a lower target of <130/80 mmHg for individuals with diabetes or chronic renal disease.[2,6,7,9] As well as lifestyle and dietary modification and treatment for co-morbidities, the initiation of antihypertensive drug treatment is often required for hypertensive patients, with regular monitoring of BP for patients with established cardiovascular disease.[40] Patient education is also necessary to support adherence to antihypertensive drug treatment and lifestyle changes.[2] Selection of a suitable antihypertensive drug is dependent on a number of factors, including concurrent diseases, such as renal disease, tolerability profile and cost.

Several classes of drugs are available for the reduction of BP (section 1); drugs that mediate BP-lowering effects via the RAS, such as the ACE inhibitors and angiotensin II receptor antagonists, are often selected because of their well established

clinical profiles and the generally low incidence of adverse events associated with these drug classes.[19] However, there are certain limitations associated with the ACE inhibitor class of drugs; for example, they only partially inhibit angiotensin II formation, and are also associated with the development of a troublesome cough in some patients. By contrast, the angiotensin II receptor antagonists appear to provide a more rational means of reducing the pressor response by selectively inhibiting the coupling of angiotensin II to the AT_1 receptor and are generally regarded as the best tolerated class of antihypertensive drugs.[19] Since their development, the angiotensin II receptor antagonists have become increasingly used in the management of patients with essential hypertension and cardiovascular disease and several drugs of this class are recommended for patients with cardiovascular co-morbidities.[9] In common with some ACE inhibitors, certain angiotensin II receptor antagonists have also shown efficacy in terms of reducing morbidity and mortality associated with cardiovascular disease, preventing end-organ damage (e.g. cardioprotective effects), and have shown beneficial effects in patients with nephropathy, in those with concomitant diabetes and in the prevention of cerebrovascular disease.[21] Angiotensin II receptor antagonists are among the drugs recommended for use in the initial and maintenance therapy of patients with essential hypertension in treatment guidelines,[2,6,7,9] and may be preferred as they have tolerability profiles that are generally similar to placebo.[22]

Azilsartan medoxomil is a recent addition to the angiotensin II receptor antagonist class of drugs, and is the eighth approved drug in this class.[41] A summary of its key features is provided in table IV.

The active moiety of azilsartan medoxomil is azilsartan, a highly selective and potent angiotensin II receptor antagonist that shows greater inhibitory effects at the AT_1 receptor than several comparator drugs of the same class. The antihypertensive effects of azilsartan medoxomil are dose-related, sustained over a 24-hour dosage interval (potentially reducing diurnal variations in BP) and durable in adults with hypertension. In animal studies and *in vitro* investigations, azilsartan demonstrated pleiotropic effects (i.e. effects beyond AT_1 receptor blockade and BP lowering) [table IV]. Approval of azilsartan medoxomil by the European Commission was based on an extensive clinical development programme, including seven randomized, double-blind, controlled trials in almost 6000 adults with essential hypertension that showed the drug significantly lowered SBP over treatment durations of 6 to 24 weeks and was more effective than maximum dosages of olmesartan medoxomil or valsartan.[42]

Table IV. Summary of the key features of azilsartan medoxomil

Oral prodrug of azilsartan, an AT_1 receptor antagonist (blocker)
Azilsartan produces greater AT_1 receptor blockade activity than several other angiotensin II receptor antagonists, including valsartan and olmesartan *in vitro*
Demonstrates pleiotropic cardioprotective effects *in vivo* and *in vitro*, e.g. beneficial effects on cardiovascular and metabolic markers
Pharmacokinetic profile allows for once-daily oral administration
More effective in reducing 24-h mean SBP than maximum approved dosages of olmesartan or valsartan over 6 weeks or valsartan over 24 weeks in randomized phase III trials
Generally well tolerated with headache and dizziness among the most common adverse events
Low rate of treatment discontinuation due to adverse events in the 24-week trial
Contraindicated during pregnancy

AT_1 = angiotensin II type 1; **SBP** = systolic blood pressure.

An important aspect of the three reviewed trials of azilsartan medoxomil (section 4) was the use of ABPM for assessments of the primary endpoint, i.e. 24-hour mean SBP at the end of the active treatment period (at week 6 or week 24), which is widely accepted as preferable to clinic BP measurements for monitoring patients with hypertension[43-46] and may be of particular value in identifying differences between angiotensin II receptor antagonists in terms of BP-lowering effects.[22] ABPM is now recommended by the National Institute for Health and Clinical Excellence for confirming diagnosis and efficacy of antihypertensive drugs.[2] This design feature distinguishes these trials from many other antihypertensive drug trials that have generally used clinic SBP or DBP as primary endpoints.[22] Although 24-hour evaluations may be more demanding than the traditional clinic BP assessments, they are highly relevant as clinical evidence supports an association between cardiovascular morbidity/mortality and ambulatory BP, and an inverse relationship between cardiovascular risk

and the extent of BP reduction from day to night has also been demonstrated.[47] The use of ABPM may also help identify patients with 'White coat' and masked hypertension.[47] Limitations of clinic SBP or DBP as primary endpoints include the small number and variability of results and problems relating to the technique used to obtain the measurements.[40] The finding that azilsartan medoxomil was more effective than the comparator agents in reducing 24-hour mean SBP may be an indication of a hierarchical response among agents in this class, possibly as a result of differences in receptor binding and dissociation rates, as shown in preclinical investigations (section 2).[15,47] The more marked antihypertensive effects seen with azilsartan medoxomil compared with olmesartan medoxomil and valsartan suggest that further clinical evaluation of the drug is warranted to evaluate its efficacy compared with that of other drugs in its class, particularly those that have demonstrated beneficial effects on clinical outcomes.

In other studies not discussed in detail in this article, azilsartan medoxomil was effective as a single agent or in combination with a diuretic in adults with hypertension (section 4.3). Of note, azilsartan medoxomil 40 or 80 mg once daily was more effective than the ACE inhibitor ramipril in a randomized, controlled 24-week trial reported as an abstract.[30] Furthermore, rates of treatment discontinuation owing to adverse events were much lower in azilsartan medoxomil than ramipril recipients. Further study of the relative efficacy of azilsartan medoxomil and other ACE inhibitors, including comparisons of effects on other measures of cardiovascular morbidity would be of interest. Azilsartan medoxomil was generally well tolerated in randomized clinical trials and the marked decreases in BP were not accompanied by an increase in clinically significant adverse events (section 5).

Across Europe, annual cardiovascular costs exceed €190 billion, of which 57% is attributed to the cost of healthcare.[4] Clinical management of hypertension is among the most common primary healthcare interventions in the UK, with annual drug costs estimated to be approximately £1 billion in 2006.[2] Pharmacoeconomic data pertaining to the use of azilsartan medoxomil in hypertension, particularly from cost-effectiveness studies comparing it with generic angiotensin II receptor antagonists, are therefore of interest. However, formal pharmacoeconomic studies of azilsartan medoxomil monotherapy have not yet been reported.

In conclusion, once-daily azilsartan medoxomil effectively lowers BP in patients with essential hypertension and has shown better antihypertensive efficacy than maximum therapeutic dosages of olmesartan medoxomil or valsartan in major trials of up to 24 weeks' duration. Azilsartan medoxomil is generally well tolerated and low rates of discontinuation due to adverse events were reported over a 24-week period, suggesting that patients are likely to persist with long-term treatment. Azilsartan medoxomil is therefore a useful and attractive new option for lowering BP in patients with essential hypertension, particularly for those not able to tolerate other antihypertensive drugs. Further studies are required to evaluate the effects of azilsartan medoxomil on cardiovascular morbidity and mortality.

Disclosure

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from the comments received were made by the author on the basis of scientific and editorial merit.

References

1. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005 Jan 15-21; 365 (9455): 217-23
2. Hypertension. Clinical management of primary hypertension in adults. NICE Clinical Guideline 127 (Aug 2011) [online]. Available from URL: http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf [Accessed 2012 July 30]
3. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003 May 14; 289 (18): 2363-9
4. European cardiovascular disease statistics 2008 [online]. Available from URL: http://www.ehnheart.org/cvd-statistics.html [Accessed 2012 July 30]

5. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet 2008 May 3; 371 (9623): 1513-8
6. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007 Jun; 28 (12): 1462-536
7. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009; 27 (11): 2121-58
8. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA 2010 May 26; 303 (20): 2043-50
9. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP. Hypertension 2003; 42 (6): 1206-52
10. World Health Organisation . Global atlas on cardiovascular disease prevention and control 2011 [online]. Available from URL: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/index.html [Accessed 2012 Jul 30]
11. Ipreziv 20 mg tablets. EU summary of product characteristics. [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002293/WC500119204.pdf [Accessed 2012 July 10]
12. French CJ, Zaman AK, Sobel BE. The angiotensin receptor blocker, azilsartan medoxomil (TAK-491), suppresses vascular wall expression of plasminogen activator inhibitor type-I protein potentially facilitating the stabilization of atherosclerotic plaques. J Cardiovasc Pharmacol 2011 Aug; 58 (2): 143-8
13. Kajiya T, Ho C, Wang J, et al. Molecular and cellular effects of azilsartan: a new generation angiotensin II receptor blocker. J Hypertens 2011; 29 (12): 2476-83
14. Zhao M, Li Y, Wang J, et al. Azilsartan treatment improves insulin sensitivity in obese spontaneously hypertensive Koletsky rats. Diabetes Obes Metab 2011 Dec; 13 (12): 1123-9
15. Ojima M, Igata H, Tanaka M, et al. In vitro antagonistic properties of a new angiotensin type 1 receptor blocker, azilsartan, in receptor binding and function studies. J Pharmacol Exp Ther 2011; 336 (3): 801-8
16. Kusumoto K, Igata H, Ojima M, et al. Antihypertensive, insulin-sensitising and renoprotective effects of a novel, potent and long-acting angiotensin II type 1 receptor blocker, azilsartan medoxomil, in rat and dog models. Eur J Pharmacol 2011 Nov 1; 669 (1-3): 84-93
17. Edarbi azilsartan medoxomil. European Public Assessment Report [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002293/WC500119207.pdf [Accessed 2012 July 3]
18. Baker WL, White WB. Azilsartan Medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother 2011 Dec; 45 (12): 1506-15
19. Volpe M, Savoia C. New treatment options in the management of hypertension: appraising the potential role of azilsartan medoxomil. Integr Blood Press Control 2012; (5): 19-25
20. Bakris GL, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. J Clin Hypertens (Greenwich) 2011; 13 (2): 81-8
21. White WB, Weber MA, Sica D, 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
22. Sica D, White WB, Weber MA, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich) 2011; 13 (7): 467-72
23. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manag 2012; 8: 133-43
24. Benson SC, Pershadsingh HA, Ho CI, et al. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity. Hypertension 2004 May; 43: 993-1002
25. Schupp M, Janke J, Clasen R, et al. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-γactivity. Circulation 2004; 109 (17): 2054-7
26. He H, Yang D, Ma L, et al. Telmisartan prevents weight gain and obesity through activation of peroxisome proliferator-activated receptor-δ-dependent pathways. Hypertension 2010 Apr; 55 (4): 869-79
27. Clemenz M, Frost N, Schupp M, et al. Liver-specific peroxisome proliferator-activated α target gene regulation by the angiotensin type 1 receptor blocker telmisartan. Diabetes 2008 May; 57 (5): 1405-13
28. Preston R, Karim A, Garg D, et al. Single-center phase I study of the single- and multiple-dose pharmacokinetics and safety of azilsartan medoxomil (AZL-M) in hepatic impairment [abstract no. PII-99]. Clin Pharmacol Ther 2012 Mar; 91 Suppl. 1: S89
29. Harrell R, Karim A, Zhang W, et al. Effects of age, gender, and race on the safety and pharmacokinetics of single and multiple doses of azilsartan medoxomil in healthy subjects [abstract no. PII-69]. Clin Pharmacol Ther 2012 Mar; 91 Suppl. 1: S78
30. Bonner G, Bakris GL, Sica D, et al. Comparison of antihypertensive efficacy of the new angiotensin receptor blocker azilsartan medoxomil with ramipril [abstract no. PP.16.112]. J Hypertens 2010; 28 Suppl. A: e 283
31. Sussman M, Leahy M, Friedman M, et al. Effects of azilsartan medoxomil versus valsartan and olmesartan medoxomil on the achievement of systolic blood pressure goals among hypertensive patients with diabetes [abstract no. PCV21]. Value Health 2011; 14 (3): A36
32. Menzin J, Leahy MJ, Friedman M, et al. Effects of azilsartan medoxomil versus valsartan and olmesartan medoxomil on the achievement of systolic blood pressure goals in essential hypertension [abstract]. J Manag Care Pharm 2011; 17 (3): 247
33. Sica D, Bakris G, White WB, et al. New angiotensin II receptor blocker azilsartan medoxomil coadministered with chlorthalidone provides potent blood pressure reduction in stage 2 hypertension [ASH abstract PO-238]. J Clin Hypertens (Greenwich) 2010; 12 Suppl. 1: A114

34. Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. Hypertension 2012 Aug; 60 (2): 310-8
35. Sica D, Bakris GL, White WB, et al. Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: a factorial study. J Clin Hypertens (Greenwich) 2012 May; 14 (5): 284-92
36. Weber MA, White WB, Sica D, et al. Antihypertensive efficacy of the new angiotensin receptor blocker azilsartan medoxomil in combination with amlodipine [abstract no. PO-241]. J Clin Hypertension (Greenwich) 2010 April; Suppl. 1: A115-116
37. Rakugi H, Enya K, Sugiura K, et al. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I-II essential hypertension: a randomized, double-blind clinical study. Hypertens Res 2012 May; 35 (5): 552-8
38. Hunt T, Karim A, Ye Z, et al. Azilsartan medoxomil does not affect the QTc interval in healthy subjects: randomized, double-blind, placebo- and positive-controlled crossover study [abstract no. PII-70]. Clin Pharmacol Ther 2012 Mar; 91 Suppl. 1: S78
39. Mancia G, Grassi G. Management of essential hypertension. Br Med Bull 2010; 94: 189-99
40. Ruilope LM. Current challenges in the clinical management of hypertension. Nat Rev Cardiol 2011 Oct 25; 9 (5): 267-75
41. Jones JD, Jackson SH, Agboton C, et al. Azilsartan medoxomil (Edarbi) the eighth angiotensin II receptor blocker. P&T 2011; 36 (10): 634-40
42. Takeda Pharmaceutical Company L. Takeda's Edarbi (azilsartan medoxomil) receives European marketing authorisation for the treatment of essential hypertension. Media Rel 2011 Dec 8
43. Hodgkinson J, Mant J, Martin U, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. Br Med J 2011 Jun 24; 342: d3621
44. de la Sierra A, Banegas JR, Segura J, et al. Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: the CARDIORISC Event study. J. Hypertension 2012 April; 30 (4): 713-9
45. Fabia MJ, Abdilla N, Oltra R, et al. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring . J Hypertens 2007 Jul; 25 (7): 1327-36
46. O'Brien E. Twenty-four-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation. J Intern Med 2011 May; 269 (5): 478-95
47. Pickering TG, White WB, Giles TD, et al. When and how to use self (home) and ambulatory blood pressure monitoring. J Amer Soc Hypertens 2008 May-Jun; 2 (3): 119-24

Correspondence: *Caroline M. Perry*, Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@springer.com