ADIS DRUG EVALUATION

Drugs 2005; 65 (13): 1851-1868
0012-6667/05/0013-1851/$39.95/0

Ramipril/Felodipine Extended-Release Fixed-Dose Combination

A Review of its Use in the Management of Essential Hypertension

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Data Selection

Sources: Medical literature published in any language since 1980 on 'ramipril felodipine ER', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'ramipril' and 'felodipine ER'. EMBASE search terms were 'ramipril' and 'felodipine ER'. AdisBase search terms were 'ramipril' and 'felodipine' and 'extended-release' or 'ramipril felodipine'. Searches were last updated 8 August 2005.

Selection: Studies in adult patients with essential hypertension who received ramipril/felodipine ER fixed-dose combination. 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: Ramipril, felodipine, extended-release, ACE inhibitors, dihydropyridine calcium channel blockers, fixed-dose combination, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Ramipril/felodipine extended release (ER) [Triapin® and Triapin Mite®, Unimax®] is a once-daily fixed-dose combination of the ACE inhibitor ramipril and the ER formulation of the dihydropyridine calcium channel antagonist felodipine. It is indicated in adult patients with essential hypertension whose blood pressure (BP) is inadequately controlled with ramipril or felodipine monotherapy. In this patient population, commercially available fixed-dose combinations (i.e. 2.5mg/2.5mg and 5mg/5mg) of ramipril and felodipine ER are more effective at controlling hypertension than the individual components used as monotherapy at the same dosages. Likewise, the 5mg/5mg combination is as effective as felodipine ER 10mg, and more effective than ramipril 10mg administered as monotherapy. The addition of low-dose ramipril plus felodipine ER (fixed-dose or combination of individual components) to the existing antihypertensive regimen also appears to provide adequate BP control and renal protection in hypertensive patients with non-diabetic chronic renal disease. In these patients, the low-dose combination of ramipril and felodipine ER was as effective as standard-dose felodipine ER, but more effective than standard-dose ramipril, in providing diastolic BP (DBP) control, and as effective as standard-dose ramipril, but more effective than standard-dose felodipine ER, in slowing the rate of regression of glomerular filtration. The ramipril/felodipine ER combination is as well tolerated as ramipril or felodipine ER monotherapy administered at the same dosages, and is better tolerated than felodipine ER monotherapy given at twice the dosage used in the combination. Overall, ramipril/felodipine ER appears to be an effective option for the treatment of adults with essential hypertension that is poorly controlled with monotherapy. In addition, a fixed, low-dose combination of ramipril/felodipine ER is a potential alternative to monotherapy for the initial management of essential hypertension.

Pharmacological Properties

Ramipril is a prodrug of the active metabolite ramiprilat, which reduces vasopressor activity and peripheral vascular resistance by inhibiting conversion of angiotensin I into angiotensin II via angiotensin-converting enzyme. Felodipine is a dihydropyridine calcium channel antagonist that inhibits the influx of calcium into vascular smooth muscle cells, causing their relaxation and vasodilation. Felodipine acts selectively on systemic, but not pulmonary arterioles and has no effect on venous vessels, whereas ramiprilat exerts its antihypertensive effects by dilating both arterial and venous blood vessels. Both agents effectively reduce systolic BP (SBP) and DBP over 24 hours in a dose-dependent manner after single-dose administration in patients with essential hypertension. Individual antihypertensive effects of ramipril and felodipine ER are significantly enhanced by their coadministration. Both drugs also exert a cardioprotective effect by causing regression of left ventricular (LV) hypertrophy in patients with essential hypertension, while preserving LV function.

Coadministration of ramipril and felodipine ER does not produce clinically relevant pharmacokinetic interactions. Both agents are well absorbed following oral administration and their bioavailabilities (44% and 16% for ramiprilat and felodipine; the bioavailability of felodipine is low because of extensive first-pass hepatic metabolism) are not affected by concurrent food intake. Ramipril is rapidly converted into ramiprilat during first-pass metabolism in the liver. Ramiprilat and felodipine ER are 56% and 99% plasma protein-bound, reach their respective peak plasma concentrations within 3 and 2.5–5 hours and have long elimination half-lives of 13–17 and 25 hours. Both ramiprilat and felodipine undergo inactivation in the liver, and the majority of a dose of each drug is eliminated as inactive metabolites in urine.

Therapeutic Efficacy

In three short-term (6–12 weeks), randomised, double-blind, multicentre trials in adult patients with essential hypertension that was not adequately controlled with monotherapy, ramipril/felodipine ER fixed-dose combinations were more effective in reducing mean SBP and DBP from baseline than both ramipril and felodipine ER monotherapies in corresponding dosages, or placebo. The ramipril/felodipine ER 5mg/5mg combination was also as effective as felodipine 10mg, and more effective than ramipril 10mg once daily, in providing SBP and DBP control over 12 weeks in this patient population. In addition, ramipril/felodipine ER 2.5mg/2.5mg once daily has been found effective in reducing SBP and DBP in previously untreated hypertensive patients in a pilot study.

A longer-term (12 months), nonblind, noncomparative study in patients with essential hypertension indicated that satisfactory BP control (a supine DBP of ≤90mm Hg or decreased by ≥10mm Hg from baseline) can be achieved in the majority of patients receiving ramipril/felodipine ER 2.5mg/2.5mg or 5mg/5mg once daily either alone (80% response rate) or in combination with one or two other antihypertensive agents (up to 99% response rate).

Low-dose combinations of ramipril and felodipine ER were also effective in controlling SBP and DBP in hypertensive patients with non-diabetic chronic renal disease in two randomised, nonblind, multicentre trials. In a trial that evaluated the fixed-dose combination, ramipril/felodipine ER 5mg/5mg once daily was significantly more effective in achieving target DBP (<90mm Hg) than ramipril 10mg once daily (86% vs 60% response rate) after a mean follow-up period of

1.83 and 1.52 years, respectively. In the other trial, which evaluated concomitant administration of ramipril 2.5mg or 5mg with felodipine ER 5mg or 10mg once daily, both the ramipril-based and the ramipril plus felodipine ER-based regimens significantly reduced SBP and DBP from baseline over 19 months' follow-up. However, the combined regimen was only significantly more effective in this regard compared with the ramipril-only regimen. These trials also showed ramipril/felodipine ER combination to be as effective as ramipril, but more effective than felodipine ER monotherapy in slowing the deterioration of renal function (i.e. the rate of regression of glomerular filtration) in hypertensive patients with non-diabetic chronic renal disease.

Tolerability

Ramipril/felodipine ER fixed-dose combinations were generally well tolerated in clinical trials in adults with essential hypertension. The most common adverse events in these trials were headache, peripheral oedema and flushing associated with felodipine ER, and dry cough associated with ramipril, and were generally mild-to-moderate in severity. In the largest, randomised, double-blind trial, the ramipril/felodipine ER 2.5mg/2.5mg combination had a tolerability profile similar to those of the individual components administered in corresponding dosages. A significantly lower overall incidence of adverse events was reported in patients receiving ramipril/felodipine ER 5mg/5mg once daily compared with recipients of felodipine ER 10mg once daily (28% vs 41%) in another randomised, double-blind trial.

1. Introduction

Hypertension is the main treatable risk factor for cardiovascular disease in developed countries, where it accounts for a loss of healthy life in an estimated 10.9% of cases.[1-3] According to a recent analysis of epidemiological surveys conducted in North America and Europe between 1986 and 1999, hypertension (defined as systolic/diastolic blood pressure [SBP/DBP] ≥140/90mm Hg or current use of antihypertensive medication) has an average age- and sex-adjusted prevalence of 28% and 44% in adults aged 35–74 years.[1] Despite a plethora of available antihypertensive agents, only 44% and 27% of hypertensive individuals in the respective regions aged 35–64 years were, on average, undergoing treatment for hypertension, and only 23% and 8% had their condition controlled (i.e. had blood pressure [BP] below 140/90mm Hg).[1,2]

Current treatment guidelines from the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[4] the European Society of Hypertension-European Society of Cardiology (ESH-ESC),[5] the World Health Organization/International Society of Hypertension (WHO/ISH)[6] and the British Hypertension Society (BHS-IV)[7] recommend initiation of antihypertensive treatment in patients with BP ≥140/90mm Hg; however, in patients with diabetes mellitus or renal, cardiovascular or cerebrovascular disease, a lower treatment threshold (BP ≥130/80mm Hg) is advocated, because of the increased risk of cardiovascular events.

The guidelines[4-7] also indicate that in order to achieve and maintain long-term "normal" (i.e. at or below target) BP, the majority of patients with essential hypertension will require the use of at least two antihypertensive agents. Multi-drug therapy can be achieved either by sequentially adding agents until an effective multi-drug regimen is established, or more simply by using a fixed-dose combination of agents. The advantages of the latter approach (e.g. better patient compliance) have been reviewed previously in *Drugs*[8] and are discussed further in section 6.

Fixed-dose combinations of an ACE inhibitor and a calcium channel antagonist are of particular

interest.[8,9] Both ACE inhibitors and calcium channel antagonists provide long-term beneficial effects on the cardiovascular complications associated with hypertension, and have favourable tolerability profiles.[10,11] However, their mechanisms of action are distinctly different and produce vascular, cardiac and renal effects that are synergistic in lowering BP and that compensate for the tendency of either drug to cause adverse effects.[8]

Ramipril/felodipine extended release (ER) [Triapin® and Triapin Mite®, Unimax®][1] is a fixed-dose combination of two well established antihypertensive agents of different drug classes: the ACE inhibitor ramipril, a prodrug of the active metabolite ramiprilat, and the ER formulation of the dihydropyridine type calcium channel antagonist felodipine. This review focuses on the use of ramipril/felodipine ER in the treatment of adult patients with essential hypertension, but also includes data in which the two agents were administered as separate formulations. An overview of the pharmacological properties of ramipril and felodipine ER, alone and/or in combination, is also provided.

2. Pharmacological Properties

The pharmacodynamic and pharmacokinetic properties of both ramipril and felodipine are well established and have been extensively reviewed previously.[9,12-18] Those data are briefly summarised herein and supplemented with additional data, where appropriate.

2.1 Pharmacodynamic Properties

The main pharmacodynamic effect of both ramipril and felodipine ER is a clinically significant reduction in SBP and DBP in patients with essential hypertension. The antihypertensive effect of each drug, which is the focus of this section, is achieved through differing mechanisms of action that are complementary, thus providing further justification for their concomitant use.

2.1.1 Ramipril

Orally administered ramipril is a well absorbed, but less effective, ACE inhibitor than its poorly absorbed but more potent metabolite ramiprilat; consequently, ramipril is used as a prodrug for ramiprilat.[12-14,18] Following oral absorption, ramipril is rapidly hydrolysed into the active metabolite ramiprilat (section 2.2.1), which is thought to exert its haemodynamic effects by competitively and reversibly inhibiting angiotensin-converting enzyme in plasma and vascular walls from converting angiotensin I to angiotensin II. Consequently, lowering of BP occurs through a decrease in the vasopressor activity of angiotensin II and a reduction in peripheral vascular resistance. Ramiprilat exerts its antihypertensive effects by dilating both arteriolar and venous blood vessels.[18,19] In the kidneys, ramiprilat predominantly dilates the vas efferens vessels, causing elevated glomerular capillary pressure to fall.[9]

In patients with essential hypertension, administration of ramipril 2.5–20mg effectively decreases SBP and DBP in a dose-dependent manner without affecting the normal circadian variation in BP or heart rate.[13] The antihypertensive effect of the drug is maximal between 4 and 8 hours and is still apparent 24 hours after single-dose administration.

Ramipril, administered at 10mg once daily, causes significant cardiovascular risk reduction in patients who are at high risk of cardiovascular events.[20] In a large (n = 9297), randomised, placebo-controlled trial in this patient population, ramipril 10mg once daily significantly reduced the rates of cardiovascular death (6.1% vs 8.1%), myocardial infarction (9.9% vs 12.3%) and stroke (3.4% vs 4.9%) after a mean 5 years' treatment (all $p < 0.001$).[20]

ACE inhibitors, including ramipril, are thought to exert cardioprotective effects by reducing left ventricular (LV) mass (a well established effect in patients with hypertension)[21,22] and by protecting against myocardial ischaemia/reperfusion injury (preclinical evidence).[13,14] A significant, dose-dependent, but BP-independent, reduction from base-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

line of LV hypertrophy and posterior wall diameter has been observed in hypertensive patients with LV hypertrophy receiving ramipril 1.25 or 5 mg/day for 6 months.[13] Likewise, treatment with ramipril 10mg once daily for 4 years significantly reduced LV mass and LV end-diastolic and end-systolic volumes, but preserved LV ejection fraction in hypertensive patients.[21]

2.1.2 Felodipine

Felodipine is a vascular-selective calcium channel antagonist of the dihydropyridine drug class that lowers BP by decreasing peripheral vascular resistance.[15-17] Felodipine inhibits the trans-sarcolemal influx of calcium into vascular smooth muscle cells, thus causing their relaxation and vasodilation.

The drug acts selectively on systemic, but not pulmonary, arterioles and has no effect on venous vessels.[15,16] Felodipine is also 100-fold more selective for vascular smooth muscle than it is for myocardial tissue, hence it has no direct effect on cardiac contractility or conduction at therapeutic antihypertensive dosages.[18] However, reflex activation of the renin-angiotensin and sympathetic nervous systems may attenuate the antihypertensive effect of felodipine by producing vasoconstriction and increasing the heart rate. On the other hand, slow and steady release of felodipine from the ER formulation prevents a sudden increase in the plasma drug concentration and a decrease in BP, and thus may prevent reflex tachycardia. Felodipine also produces a mild natriuretic and diuretic effect, thus preventing fluid retention.[15,17] At the renal level, felodipine exerts its vasodilating effect predominantly on the vas afferens vessels.[9] Felodipine has no significant effect on glomerular filtration rate (GFR) in hypertensive patients with normal renal function.[15,17] However, in patients with impaired renal function, treatment with felodipine is associated with a significant reduction from baseline in GFR.[23]

In patients with essential hypertension, felodipine 5–20mg once daily produces a significant reduction in SBP and DBP consistently over 24 hours in a dose-dependent manner.[15-18] Aging influences the response to felodipine and an increase in the maximum drug effect (i.e. a reduction of ≈4mm Hg per decade in sitting DBP) has been predicted with increasing age, thus suggesting the use of a lower starting dose for the treatment of hypertension in the elderly.[24]

Table I. Overview of the pharmacodynamic properties of ramipril (RAM) and felodipine extended release (FEL), alone and in combination, in hypertensive patients (pts)

Parameter	RAM	FEL	RAM/FEL
Haemodynamic effects			
Blood pressure[14,15,30]	↓	↓	↓↓
Peripheral vascular resistance[14,15]	↓	↓ (reflex ↑)	↓
Cardiac output[15,21]	=	↑	↑
Cardiac effects			
Heart rate[13,30]	=	acute ↑	=
LVM[12,21]	↓	↓	↓
Renal effects			
GFR[15,18]	=[a] or ↑[b]	↓[a] or =[b]	=[a] or ↑[b]
Plasma renin activity[14,15]	↑	↑	↑
Plasma aldosterone levels[14,15,18]	↓	=	↓

a Pts with chronic glomerulonephritis.

b Pts with normal renal function.

GFR = glomerular filtration rate; **LVM** = left ventricular mass; ↑ indicates increase; ↓ indicates decrease; = indicates no change.

Felodipine ER 5mg[25] and 10mg[25,26] once daily has also been shown to progressively induce significant reductions in LV mass index and posterior wall thickness after 3–12 months of treatment in patients with essential hypertension, while maintaining LV systolic performance. The effect on LV hypertrophy regression was independent of the observed, significant SBP and DBP reduction, which was maintained throughout treatment.[25,26]

2.1.3 Ramipril/Felodipine Extended Release (ER)

The antihypertensive effects of ramipril and felodipine ER are significantly enhanced when the individual drugs are combined (see section 3). The synergy possibly occurs because the natriuretic effect of felodipine reinforces the antihypertensive effect of ramipril,[8,9] and also because ramipril inhibits the formation of angiotensin II, which is know to activate the influx of calcium into vascular smooth muscle cells, a process specifically blocked by felodipine.

Additional (potential) benefits of the ramipril/felodipine combination compared with the two

drugs used as monotherapy are outlined in table I. For example, reflex/compensatory tachycardia induced by felodipine ER may be prevented or attenuated by ramipril, as shown in healthy volunteers. The lack of renoprotective effect from felodipine in hypertensive patients with chronic renal disease (section 2.1.2), may be compensated for by the better preservation of GFR offered by ramipril. The renoprotective effect offered by the combination of the two agents may in part be explained by their differential actions on afferent and efferent glomerular blood vessels (section 2.1.1 and section 2.1.2), which relieve the pressure in the glomerulus from both sides.

Meta-analyses of randomised, double-blind trials in patients with essential hypertension show that treatment with ACE inhibitors, including ramipril, or calcium channel antagonists, including felodipine, is associated with significantly greater regression of LV hypertrophy than treatment with β-blockers (β-drenoceptor antagonists) [both $p < 0.05$].[27-29] Whether the fixed-dose combination of ramipril and felodipine ER has an even greater effect on reversal of LV hypertrophy than the individual components as monotherapy is yet to be confirmed in clinical trials.

Table II. Summary of clinically important pharmacodynamic interactions observed when ramipril (RAM) and/or felodipine extended release (FEL) are coadministered with other agents[19,32,33]

Physiological effect	Agents
Hypotension (potentiated antihypertensive effect)	Antihypertensives, nitrates, antipsychotics, narcotics, anaesthetics, loop diuretics, alcohol (with RAM/FEL)
Reduced antihypertensive effect	Vasopressor sympathomimetics (with RAM/FEL); NSAIDs (with RAM)
Potentiated hypoglycaemic effect	Insulin, oral antidiabetics (with RAM)
Hyperkalaemia	Potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes (with RAM/FEL); NSAIDs (with RAM)
Neutropenia and agranulocytosis	Allopurinol, cytostatics, immunosuppressants, procainamide, systemic corticosteroids (with RAM)

Table III. Summary of the pharmacokinetic properties of ramiprilat, the active metabolite of ramipril, and felodipine

Parameter [dose]	Ramiprilat	Felodipine
Bioavailability (%)[18]	44	16
Plasma protein binding (%)[18]	56	99
C_{max} (μg/L) [10mg][12,33]	33.6	2.7[a]
t_{max} (h) [10mg][12,33]	3	2.5–5[a]
Vd (L/kg)[18]	1.2	9.7[b]
CL (mL/min/kg)[18]	1.1	12[b]
$t_{½β}$ (h)[19,31]	13–17[c]	25[a]
Route of elimination[d] (%)[12,33]	Renal 60, biliary 40	Renal 70, biliary 10

a Extended-release formulation.

b Immediate-release formulation.

c Within therapeutic concentration range.

d Primarily as inactive metabolites.

C_{max} = peak plasma concentration; **CL** = total body clearance; **$t_{½β}$** = elimination half-life; **t_{max}** = time to C_{max}; **Vd** = volume of distribution.

2.1.4 Pharmacodynamic Interactions

Clinically important pharmacodynamic interactions occurring between ramipril or felodipine ER and a number of other drugs are presented in table II. As a consequence of these interactions, concomitant administration of ramipril/felodipine ER is not recommended with some drugs (e.g. potassium-sparing diuretics, potassium supplements, potent inducers or inhibitors of cytochrome P450 [CYP] 3A4), while close monitoring or dosage adjustments may be necessary with others (see the manufacturer's prescribing information[19,31] for more details). Coadministration of ramipril with propranolol has no adverse effects on BP and heart rate, and with warfarin or phenprocoumon has no adverse effects on the state of anticoagulation.[32]

2.2 Pharmacokinetic Properties

Combined administration of ramipril and felodipine ER does not appear to produce clinically significant alterations in the pharmacokinetic parameters of either drug.[19,31] As the pharmacokinetic properties of both ramipril and felodipine have been extensively reviewed previously,[12-16,18] this section provides a brief overview of the pharmacokinetics of ramipril and felodipine as single-drug preparations (summarised in table III).

2.2.1 Ramipril

Following oral administration, ≈56% of a ramipril dose is absorbed.[12] Concomitant food intake reduces the rate of absorption of ramipril, but does not affect its overall bioavailability. After absorption, ramipril is rapidly and almost completely converted into the active diacid metabolite ramiprilat via hydrolysis of the ester group during first-pass metabolism in the liver.[12,32] There is a linear relationship between peak plasma concentrations (C_{max}) of ramipril and its active metabolite over the therapeutic dose range of the parent drug.[12,32]

After reaching C_{max}, plasma concentrations of ramiprilat decline in a triphasic manner.[12,32] The initial rapid decline phase (distribution half-life [$t_{1/2}\alpha$] of 1.1–4.5 hours) represents distribution and subsequent binding of the drug to plasma and tissue angiotensin-converting enzyme.[12] At steady state, the $t_{1/2}$ of ramiprilat within the therapeutic concentration range is 13–17 hours (table III). As the drug slowly dissociates from the enzyme, ramiprilat undergoes two elimination phases: the apparent phase has an elimination $t_{1/2}\beta 1$ of 9–18 hours and corresponds to clearance of unbound ramiprilat, while the terminal phase ($t_{1/2}\beta 2$ of up to 110 hours) probably reflects the binding/dissociation kinetics of the ramiprilat/angiotensin-converting enzyme complex.[12] Despite the length of the latter phase, clinically significant accumulation of ramiprilat does not occur with once-daily administration in patients with normal renal function.[13] Both ramiprilat and the parent drug are conjugated to their respective inactive glucuronides and diketopiperazine derivatives, all of which are predominantly eliminated via the kidneys (table III). Only a small fraction (<2%) of ramipril is excreted unchanged in urine.[13]

The pharmacokinetics of ramiprilat are significantly affected by renal functional impairment; the clearance and elimination rate are directly proportional to the degree of renal impairment, while plasma concentrations are inversely related to renal function.[12,13] Thus, ramipril dosage adjustments (based on creatinine clearance) are necessary in this patient population.[32] Hepatic impairment slows the metabolic conversion of ramipril into ramiprilat (by up to 50% of normal in patients with cirrhosis of the liver), but therapeutic C_{max} levels of ramiprilat are still achieved in the majority of these patients.[12,32]

2.2.2 Felodipine

Felodipine administered as an ER oral tablet is completely absorbed from the gastrointestinal tract;[15,18] the process is unaffected by concomitant food intake.[19,31] However, oral bioavailability of felodipine is significantly reduced (table III) due to extensive hepatic first-pass metabolism, which is also responsible for marked interindividual variability in felodipine plasma concentrations (≈3-fold),[15] as well as in other pharmacokinetic parameters (e.g. 34% and 35% in the drug's clearance [CL] and volume of distribution [Vd]).[24] Therapeutic plasma concentrations of felodipine for DBP reduction range from 1 to 50 μg/L, and the plasma concentration producing 50% of maximal BP reduction is 3 μg/L.[18] When administered as an immediate-release formulation, felodipine initially distributes rapidly (with a $t_{1/2}\alpha 1$ of ≈6 minutes) to total body water (Vd of 0.6 L/kg), and then redistributes to slower equilibrating tissues with a distribution $t_{1/2}\alpha 2$ of 1.5 hours[15] and a terminal Vd of ≈10 L/kg (table III). With the ER formulation, absorption and distribution phases of felodipine cannot be distinguished, since these extend beyond 12 hours.[15] Felodipine is extensively bound to plasma proteins (table III).

Felodipine is almost completely metabolised in the liver.[15] Inactivation of the drug starts with conversion to a pyridine analogue by microsomal CYP enzymes, and continues mainly via oxidation, resulting in at least ten haemodynamically inactive metabolites[15] that are excreted predominantly in urine (table III). Less than 0.5% of a felodipine dose is excreted unchanged in urine.[19,31] Despite a slower (25 hours) $t_{1/2}\beta$ of felodipine ER (table III) compared with that of the immediate-release formulation (11.4 hours),[18] the drug does not accumulate during long-term treatment.[19,31]

The pharmacokinetics of felodipine are affected by hepatic, but not renal impairment. Plasma drug concentrations were significantly higher in patients with hepatic cirrhosis or congestive heart failure than in healthy volunteers after single-dose administration.[15,18,19,31] Consequently, felodipine dosage

adjustment is necessary in patients with hepatic impairment.[33]

Age also influences the pharmacokinetic properties of felodipine.[15,16,18] There is a linear decline in CL of felodipine with increasing age until 60 years (remaining constant thereafter),[24] with corresponding increases in plasma drug concentrations and $t_{1/2}\beta$ values.[15,16] However, the magnitude of these changes lies within that of the interindividual variability of felodipine pharmacokinetics, thus requiring no dosage adjustments in the elderly.[15,16]

2.2.3 Pharmacokinetic Interactions

Clinically important pharmacokinetic interactions between ramipril or felodipine ER and a number of other agents and nutrients are presented in table IV. As a consequence of these interactions, close monitoring or dosage adjustments may be required (see manufacturers' prescribing information[19,31] for more detail). No significant drug interactions were observed between ramipril or ramiprilat and antacids, cimetidine, digoxin, furosemide, indomethacin, phenprocoumon or simvastatin.[32] Likewise, concomitant administration of felodipine with digoxin, indomethacin, metoprolol or spironolactone was not associated with significant pharmacokinetic interactions.[33]

Table IV. Clinically relevant pharmacokinetic interactions between ramipril or felodipine extended release (ER) and various other agents observed when administered concomitantly[19,32-34]

Pharmacokinetic effect	Concomitant agent
Effect of ramipril or felodipine ER on concomitant agent	
Ramipril ↓ excretion	Lithium
Felodipine ↑ serum concentration	Tacrolimus
Effect of concomitant agent on ramipril or felodipine ER	
↓ Plasma felodipine concentrations	CYP3A4 inducers (carbamazepine, phenytoin, phenobarbital, rifampicin [rifampin], St John's wort [*Hypericum perforatum*])
↑ Plasma felodipine concentrations	CYP3A4 inhibitors (azole antifungals, macrolides, cimetidine, telithromycin, HIV protease inhibitors, grapefruit juice), high-fat food

CYP = cytochrome P450; ↑ indicates increase; ↓ indicates decrease.

3. Therapeutic Efficacy

The clinical efficacy of ramipril/felodipine ER fixed-dose combinations has been evaluated in several trials in patients with essential hypertension with either no renal disease[35-39] or non-diabetic chronic renal disease.[40,41] All but one trial (a pilot study on first-line drug use)[38] evaluated the efficacy of the combination as a second-line treatment option (i.e. in hypertensive patients with BP not controlled with current medication[s])[35-37,39,40] or requiring multi-drug regimens for adequate BP control[41]). In all these trials, patients underwent a run-in phase with either placebo (of 2,[36] 4[37] or 2–4[35,39] weeks) or an active antihypertensive treatment (of 2–4[40] or 6[41] weeks). Trials in patients with normal renal function (section 3.1) assessed only the control of SBP and DBP in order to determine the clinical efficacy of drug regimens, whereas trials in patients with chronic renal disease (section 3.2) used progression of renal impairment as the primary (section 3.2.2) and BP control as the secondary efficacy endpoints (section 3.2.1). Most trials were fully published.[35,37,39-41]

In all trials, the antihypertensive effect of drug regimens was evaluated using a variety of endpoints, including the reduction from baseline in 24-hour ambulatory BP,[36,38] the mean trough (24 hours after administration) reduction in supine[35,39,40] and standing[35,37,39,40] or sitting[41] BP, and the mean arterial pressure averaged from supine and standing measurements.[35] In four trials, patients were classified as responders if office BP achieved was <140/90mm Hg,[36] final supine DBP was ≤90mm Hg or reduced by ≥10mm Hg from baseline,[37,39] or DBP was <90mm Hg.[40]

Where specified, trials included only adult patients (aged 18–79 years) who generally had mild-to-moderate hypertension (defined as supine DBP within the 95–115mm Hg[37,39] or 100–115mm Hg[35] range, or ≥95mm Hg,[40] or as daytime ambulatory SBP/DBP >130/80mm Hg[36]); patients with moderate-to-severe hypertension (grade 2 and 3; actual BP values not specified) were included in the pilot study.[38] In comparative trials (section 3.1.1 and section 3.2), treatment groups

were well matched at baseline for all patient characteristics. Where stated, patients were excluded from studies evaluating the antihypertensive efficacy of ramipril/felodipine ER if they had a history of severe hypertension,[37,39,41] acute myocardial infarction or cerebrovascular accident within 6 months prior to enrolment,[37,39-41] heart failure or angina pectoris,[37,39,40] renovascular disease/renal artery stenosis[37,39-41] or diabetes mellitus,[37,40,41] or if they received treatment with NSAIDs.[37,40,41] In studies assessing the renoprotective effect of ramipril/felodipine ER,[40,41] patients were also excluded if they had bladder dysfunction or obstructive uropathy, poor tolerance to ACE inhibitors or dihydropyridine calcium channel antagonists or were receiving treatment with corticosteroid or immunosuppressive drugs.

3.1 In Patients with Essential Hypertension

The short-term (6–12 weeks) effect of ramipril/felodipine ER fixed-dose combinations on BP control in patients with essential hypertension uncontrolled with single-agent therapy has been compared with those of ramipril and felodipine ER monotherapies[35-37] and versus placebo[35] in three randomised, double-blind, multicentre trials (section 3.1.1). The short-term (4 weeks) efficacy of this drug combination as the primary treatment for essential hypertension has also been evaluated in a randomised, pilot study.[38] The assessment of the longer-term (12 months), BP-controlling effect of the combination was assessed in a noncomparative study (section 3.1.2).[39]

3.1.1 Comparisons with Placebo and/or Ramipril or Felodipine ER Monotherapy

In adult patients with essential hypertension in whom BP could not be controlled with monotherapy, fixed low-dose combinations of ramipril and felodipine ER administered once daily have demonstrated significant reductions in both SBP and DBP from baseline[37] (table V) and versus placebo (p-values not reported).[35] Both of the two commercially available ramipril/felodipine ER dose combinations (see section 5) produced significantly greater reductions from baseline in mean supine SBP after 6[35] or 12[37] weeks of once-daily treatment than its individual components administered in equal doses (table V). This was also true with regard to mean DBP in the 6-week trial.[35] However, in the 12-week trial, the difference in DBP reduction was statistically significant only versus felodipine ER 2.5mg, but not ramipril 2.5mg once daily.[37] Similar results were reported for the reduction from baseline in the averaged supine and standing arterial pressure in one trial (13.2 vs 6.1 and 8.3mm Hg; $p < 0.001$ and $p < 0.05$ vs ramipril and felodipine ER, respectively),[35] and the standing BPs in the other ($p < 0.0001$ for both comparisons; actual values not reported).[37] With regard to BP control, another study[36] also showed ramipril/felodipine ER 5mg/5mg to be superior to ramipril 10mg as monotherapy after 12 weeks of once-daily administration; the effect on SBP and DBP control was similar for the ramipril/felodipine ER combination and felodipine ER 10mg once daily.

The proportion of patients responding (see table V for definition) to treatment with combination therapy was not significantly greater than that with either equal (statistical analysis not reported)[37] or double ($p = 0.056$)[36] doses of individual components in monotherapy (table V).

The effectiveness of ramipril/felodipine ER fixed-dose combination as first-line therapy of essential hypertension has been suggested by a randomised, prospective, multicentre pilot study (termed IndComb) in 150 patients with grade 2 or 3 hypertension.[38] After 4 weeks of treatment, reductions in SBP and DBP were significantly greater with ramipril/felodipine ER 2.5mg/2.5mg than with each individual component used as monotherapy.

3.1.2 Noncomparative Study

Ramipril/felodipine ER fixed-dose combination produced longer-term satisfactory BP control in the majority of 150 adult patients with essential hypertension (DBP of 95–115mm Hg) in a nonblind, noncomparative study.[39] Following 2–4 weeks of placebo run-in, patients received once-daily antihypertensive drug treatment for up to 12 months that was assigned using a step-wise, incremental algorithm for BP control. Treatment was initiated

Table V. Comparative efficacy of ramipril/felodipine extended release (RAM/FEL) versus RAM, FEL or placebo (PL) in adult patients (pts) with mild-to-moderate essential hypertension (EH). Summary of intent-to-treat analyses from randomised, double-blind, multicentre trials[35-37] in pts who had previously received an inadequate single-agent treatment for EH. All regimens were administered once daily. From a study reporting additional comparisons,[35] only data for the commercially available fixed-dose combination are presented

Study	Treatment		No. of pts	Mean SBP/DBP (mmHg)[a]		Responders (%)[b]
	duration (wk)[c]	regimen (mg/day)		at baseline	reduction at endpoint	
Placebo-controlled trial[d]						
Scholze et al.[35]	6	RAM/FEL 5/5	44	NR[e]	19.7**††/11.0***†	NR
		RAM 5	42	NR[e]	11.0/5.2	NR
		FEL 5	44	NR[e]	10.2/8.3	NR
		PL	43	NR[e]	3.7/2.6	NR
Comparisons versus RAM and FEL monotherapies						
Coca et al.[36][f]	12	RAM/FEL 5/5	NR[g]	>130/85[h]	16.5*/11.4**	46
		RAM 10	NR[g]	>130/85[h]	9.3/7.2	25
		FEL 10	NR[g]	>130/85[h]	16.7**/11.9***	28
Poisson et al.[37]	12	RAM/FEL 2.5/2.5	212	163.5/101.9	14.8‡§[i]/11.4‡†[i]	65
		RAM 2.5	212	166.7/102.1	11.2‡/9.8‡	56
		FEL 2.5	207	165.2/102.1	10.8‡/9.1‡	53

a Supine BP measurement was specified in fully published studies.[35,37]

b Pts with office BP <140/90mm Hg,[36] or final supine DBP ≤90mm Hg or reduction from baseline of ≥10mm Hg.[37]

c Prior to randomisation, pts underwent a PL run-in of 2,[36] 4[37] or 2–4wk.[35,39]

d Statistical analyses of comparisons versus PL were not reported.

e All pts had DBP of 110–115mm Hg at baseline.

f Abstract.

g A total of 154 pts were randomised to three treatment groups.

h Daytime ambulatory BP monitoring.

i Mean difference between combination therapy and monotherapy was adjusted for treatment, pool and treatment-pool interaction.

BP = blood pressure; **DBP** = diastolic BP; **NR** = not reported; **SBP** = systolic BP; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs RAM; † $p < 0.05$, †† $p < 0.01$ vs FEL; ‡ $p < 0.0001$ vs baseline; § = statistically significant vs monotherapy components.

with ramipril/felodipine ER 2.5mg/2.5mg and the dosage was increased to 5mg/5mg in a fixed-dose combination if DBP remained >90mm Hg after 1 month. Using the same criteria, metoprolol controlled release 50 mg/day or hydrochlorothiazide 12.5 mg/day or both agents were added to the drug regimen if BP was still uncontrolled after 3 or 6 months, respectively. No other antihypertensive drugs were allowed.

After 12 months, all 147 patients who received ramipril/felodipine ER-based treatment had significantly reduced mean SBP and DBP assessed in both supine (by 30.1 and 18.7mm Hg) and standing (by 33.4 and 18.1mm Hg) positions ($p < 0.001$ for all comparisons vs baseline). More importantly, a response to treatment (defined as a supine DBP of ≤90mm Hg or decreased by ≥10mm Hg) was achieved in 98.6% of patients overall, 80.3% of whom received the ramipril/felodipine ER fixed-dose combination alone (45.6% with 2.5mg and 34.7% with 5mg of each drug), whereas only 17.0% and 2.7% of patients required addition of the third and fourth drug to the regimen for adequate BP control.

3.2 In Patients with Non-Diabetic Chronic Renal Disease

The BP-controlling and renoprotective effects of low-dose combinations of ramipril and felodipine ER have been investigated in two randomised, nonblind, multicentre studies in patients with hypertension and non-diabetic renal disease.[40,41]

In the first study,[40] patients with GFR below age-adjusted normal and uncontrolled hypertension (baseline DBP ≥95mm Hg) who had already received treatment with a diuretic and a β-blocker for

1 month were randomised to additional once-daily treatment with ramipril/felodipine ER 1.25mg/1.25mg–10mg/10mg fixed-dose combination (n = 51) and ramipril 2.5–20mg or felodipine ER 2.5–20mg monotherapy (n = 53 and 54). At mean follow-up of 1.83, 1.52 and 1.83 years, patients in the ramipril/felodipine ER, ramipril and felodipine ER treatment groups were receiving mean daily doses of 5mg/5mg, 10mg and 9mg, respectively.

The second study (termed REIN-2)[41] included patients with controlled hypertension (baseline DBP <90mm Hg) receiving background treatment with ramipril 2.5mg (16%) or 5mg (84%) once daily and concomitant antihypertensive drugs (other than felodipine and angiotensin II receptor antagonists) and a reduced creatinine clearance with persistent proteinuria. These patients were randomised to conventional (DBP <90mm Hg; n = 168 evaluable) or intensified (SBP/DBP <130/80mm Hg; n = 167 evaluable) BP control (the latter was achieved with the addition of felodipine ER 5mg in approximately one-third and 10mg in about two-thirds of patients) and were followed-up for a median of 19 months.

3.2.1 Blood Pressure Control

Antihypertensive drug regimens based on low-dose combinations of ramipril and felodipine ER seem to offer effective BP control in hypertensive patients with non-diabetic chronic renal disease.

In the first study,[40] recipients of ramipril/felodipine ER 5mg/5mg, ramipril 10mg or felodipine ER 9mg once daily (all dosages are mean values) all had median SBP and DBP reduced significantly from baseline at study endpoints (figure 1; all $p < 0.001$), although differences between combination therapy and each monotherapy were not statistically significant. However, the response to treatment (defined as DBP <90mm Hg) was significantly more common in ramipril/felodipine than in ramipril monotherapy recipients (86% vs 60%; $p < 0.05$).[40]

In the second study,[41] both ramipril-based (conventional) and the ramipril plus felodipine ER-based (intensified) BP-control regimens produced significant lowering of SBP and DBP from baseline (figure 1). Moreover, the combined ramipril plus felodipine ER regimen was significantly more effective in reducing BP than the ramipril-only regimen ($p < 0.005$ and $p < 0.0001$ for SBP and DBP; figure 1)

3.2.2 Progression of Renal Disease

Combining ramipril with felodipine ER for the treatment of essential hypertension in patients with concomitant non-diabetic chronic renal disease seems to have a longer-term protective effect against renal disease progression similar to that of ramipril alone, but significantly greater than that with felodipine ER alone.

In the first study,[40] evaluable patients (n = 45) receiving ramipril/felodipine ER-based treatment had a significantly slower median rate of regression

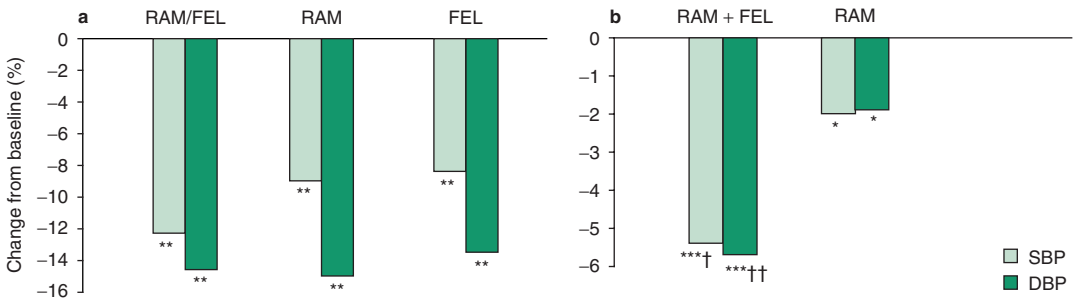

Fig. 1. Effect of ramipril/felodipine extended release (RAM/FEL) combinations on systolic and diastolic blood pressure (SBP and DBP) in hypertensive patients (pts) with non-diabetic chronic renal disease. Presented are intent-to-treat analyses of endpoint results from two randomised, nonblind trials.[40,41] In addition to pre-existing treatments, pts in (**a**), who had baseline DBP ≥95mm Hg, received an average once-daily dose of RAM/FEL 5mg/5mg (n = 51), RAM 10mg (n = 53) or FEL 9mg (n = 54) at mean 1.83, 1.52 and 1.83 years of follow-up, respectively,[40] while pts in (**b**) received once-daily RAM 2.5–5mg (n = 168) or RAM 2.5–5mg plus FEL 5–10mg (n = 167) for a median of 19 months.[41] * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ vs baseline; † $p < 0.005$, †† $p < 0.0001$ vs RAM-based therapy.

of glomerular filtration compared with patients (n = 50) in the felodipine ER group (−3.8 vs −6.0 mL/min/year; $p < 0.05$), but had a similar median rate to that in patients (n = 41) in the ramipril group (−3.8 vs −5.8 mL/min/year). Nevertheless, a significant decrease from baseline in the GFR occurred, despite treatment in all three groups.

In the second study,[41] the median rate of glomerular filtration decline in the ramipril plus felodipine ER (intensified BP-control) group (n = 93 evaluable patients) was similar to that in the ramipril-only (conventional BP-control) group (n = 80 evaluable patients) [−4.6 vs −5.0 mL/min/year, reported as −0.22 vs −0.24 mL/min/1.73m^2/month]. Consequently, the rate of progression to end-stage renal disease (primary endpoint) over the median 19 months' follow-up was similar in recipients of intensified or conventional BP control (23% vs 20%).

4. Tolerability

Commercially available ramipril/felodipine ER fixed-dose combinations (see section 5 for details) were generally well tolerated in adults with essential hypertension, where reported in clinical trials[35,37,39] described in section 3.

Headache, peripheral oedema and flushing are the most common adverse events associated with felodipine ER, and dry cough with the use of ramipril, as noted in the manufacturer's prescribing information for felodipine ER,[33] ramipril[32] and the fixed-dose combination,[19,31] and as reported in clinical trials in adults treated with ramipril/felodipine ER.[35,37,39] In two of the clinical trials,[37,39] adverse events were generally mild-to-moderate in severity.

In the largest randomised, double-blind trial in patients with essential hypertension that compared once-daily low-dose ramipril/felodipine ER with ramipril and felodipine ER monotherapies,[37] all regimens had similar tolerability profiles (figure 2); study withdrawal rates possibly related to treatment were 5.1%, 0.5% and 3.8% in the combination, ramipril and felodipine ER treatment groups, respectively. However, in another randomised, double-blind trial in patients with essential hypertension,[36] a significantly lower overall incidence of adverse events was reported by patients receiving ramipril/felodipine ER 5mg/5mg once daily compared with recipients of once-daily felodipine ER 10mg (standard monotherapy dosage) [28% vs 41%; $p < 0.01$].

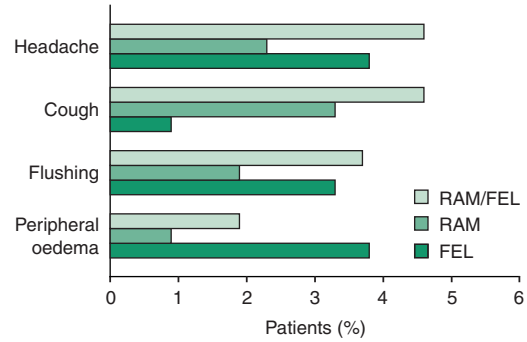

Fig. 2. Tolerability profile of ramipril/felodipine extended release (RAM/FEL) fixed-dose combination versus RAM or FEL monotherapy in patients with essential hypertension. Incidence of the most common adverse events possibly related to treatment in a randomised, double-blind trial in adults receiving RAM/FEL 2.5mg/2.5mg (n = 216), RAM 2.5mg (n = 213) or FEL 2.5mg (n = 213) for 12 weeks.[37]

A pilot study on the first-line use of ramipril/felodipine ER fixed-dose combination as antihypertensive therapy[38] showed no significant difference in the incidence and severity of adverse events between recipients of ramipril/felodipine ER 2.5mg/2.5mg, ramipril 2.5mg and felodipine ER 2.5mg (actual results and statistical analyses not reported).

5. Dosage and Administration

The ramipril/felodipine ER fixed-dose combination is approved in Europe for the treatment of essential hypertension in adults whose BP cannot be adequately controlled with maximum recommended dosages of ramipril or felodipine ER monotherapy.[19,31] Recommended ramipril and felodipine ER dosages administered once daily in a single-tablet formulation are 2.5mg/2.5mg and 5mg/5mg (daily maximum).[19,31]

The use of ramipril/felodipine ER combination is contraindicated during pregnancy and lactation and in patients with severely impaired renal or hepatic

function, hypersensitivity to either felodipine (or other dihydropyridine calcium channel antagonists) or ramipril (or other ACE inhibitors), unstable haemodynamic conditions (i.e. acute myocardial infarction, unstable angina pectoris, untreated heart failure, cardiovascular shock or stroke) or with a history of angioneurotic oedema.[19,31] Ramipril/felodipine ER should not be used in children due to the lack of clinical experience in this population.[19,31] For specific recommendations in other patient populations, warnings, precautions and drug interactions in addition to those described in section 2.1.4 and section 2.2.3, see the manufacturers' prescribing information.[19,31]

6. Place of Ramipril/Felodipine ER in the Management of Essential Hypertension

The primary goal in the treatment of patients with hypertension is to minimise the long-term risk of cardiovascular morbidity and mortality.[4-7] This is achieved by combined implementation of non-pharmacological (i.e. lifestyle modifications, such as smoking cessation, reduction of weight and of salt and excessive alcohol intake, regular physical exercise, and a healthy diet [increase in fruit and vegetable intake and reduction in saturated and total fat intake]) and pharmacological therapeutic measures. Although the former measures are advised in all patients, regardless of their BP levels, pharmacological measures are specifically utilised in patients with established hypertension or those in whom high normal BP is associated with pre-existing cardiovascular or cerebrovascular disease, diabetes or chronic renal disease.

The pharmacological treatment of hypertension can be initiated either with low-dose monotherapy or combination therapy.[4-7] The advantage of the former approach is that it provides the best means for individualising treatment with the most effective and best tolerated drugs for each patient. However, this approach is resource-intensive and time-consuming, which may result in low patient compliance. Initiating treatment of hypertension with a low-dose combination of two agents has several advantages,[8,42] most notable of which are:

- better control of BP and its complications with the use of agents with different mechanisms of action;
- better tolerability (fewer adverse events) with the use of agents in the low-dose range; and
- better patient compliance with the use of fixed-dose combinations of two agents as a single formulation.

Despite potentially exposing the patient to the use of an unnecessary agent, it may be sensible to use this latter approach to initiate antihypertensive therapy in the light of results of large-scale randomised, double-blind clinical trials,[43,44] which showed that at least 40% of patients with grade 1 or 2 hypertension,[43] and up to 60–75% of patients with grade 2 or 3 hypertension[5] require at least two drugs for adequate BP control long term (>3.8 years on average).

In the US,[4,45] the preferred initial drugs of choice for the treatment of most hypertensive patients are thiazide diuretics, used either alone or in combination with one of the other drug classes (i.e. β-blockers, ACE inhibitors, calcium channel antagonists or angiotensin-receptor antagonists). These recommendations from the JNC 7 are based on a report from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),[43] which concluded that thiazide diuretics are less expensive than, and superior to, ACE inhibitors or calcium channel antagonists in preventing some major forms/complications of cardiovascular disease (e.g. heart failure, angina pectoris and stroke), although all agents had similar effects on the primary efficacy outcome of fatal and non-fatal coronary disease combined. WHO/ISH guidelines have a similar approach for the treatment of essential hypertension in patients without compelling indications for a particular drug class.[6]

European (ESH-ESC) guidelines[5] have shifted the focus from identifying the initial drug of choice to the main goal of achieving target BPs and are, thereby, less prescriptive and offer wider possibilities for drug combinations than the US guidelines. They also offer a choice of initiating the treatment of

hypertension with a single agent or a two-drug combination, either administered at low dose(s).

The British (BHS-IV) guidelines[7] are in partial agreement with the European guidelines in that the main benefit from antihypertensive agents lies in the achieved BP, rather than in the choice of therapy. However, in order to achieve target BPs, the British guidelines firmly advocate the use of at least two antihypertensive agents in most patients by applying the AB/CD treatment algorithm, which states that drugs that inhibit the renin-angiotensin system (i.e. ACE inhibitors and angiotensin II receptor antagonists [A] or β-blockers [B]) should be combined with those that do not inhibit it (calcium channel antagonists [C] or diuretics [D]).

For hypertensive patients with special/high-risk conditions, the use of specific antihypertensive drug regimens should be guided by compelling indications (table VI).

The fixed-dose combination of ramipril/felodipine ER combines ACE inhibition with calcium channel antagonism to provide effective reduction of BP in patients with essential hypertension (section 3). Both agents cause vasodilation and reduce peripheral vascular resistance via mechanisms that are different, but complementary (section 2.1).

Table VI. Guidelines[4,5,7] for the use of specific classes of antihypertensive agents in hypertensive patients (pts) with special/high-risk conditions

Recommended drug class	Compelling indications
ACE inhibitors	CHF, LV dysfunction, post MI, high CAD risk, diabetes mellitus, chronic renal disease, recurrent stroke prevention
Calcium channel antagonists	High CAD risk/angina pectoris, diabetes, isolated systolic hypertension, elderly pts, pregnancy
Thiazide diuretics	CHF, high CAD risk, diabetes, isolated systolic hypertension, recurrent stroke prevention, elderly pts
β-blockers	CHF, high CAD risk/angina pectoris, post MI, diabetes, pregnancy
Angiotensin II receptor antagonists	CHF, LV hypertrophy, post MI, diabetes, chronic renal disease

CAD = coronary artery disease; **CHF** = congestive heart failure; **LV** = left venticular; **MI** = myocardial infarction.

The state of negative sodium balance induced by the natriuretic activity of felodipine potentially facilitates the antihypertensive effects of ramipril. Reflex sympathetic activity (e.g. increased heart rate) and renin release induced by felodipine become counterbalanced, respectively, by modulation of sympathetic activity/responsiveness and antagonism of the renin-angiotensin system effected by ACE inhibition from ramipril (section 2.1.3). Likewise, combined administration of ramipril and felodipine ER may also have a renoprotective effect in hypertensive patients (section 2.1.3).

The pharmacokinetics of ramipril and felodipine ER are also complementary and not altered by their coadministration (section 2.2). Both drugs are administered orally and their bioavailabilities are not significantly affected by concurrent food intake. They both undergo extensive hepatic metabolism, although via different mechanisms, and are predominantly eliminated in urine in inactive forms; a dosage adjustment may be required in patients with hepatic or renal functional impairment. Both ramipril and felodipine ER have long $t_{1/2}$ values (section 2.2), accounting for the long duration of action and providing BP control over a 24-hour period (sections 2.1.1 and 2.1.2), thus allowing for once-daily administration of the fixed-dose combination. Further advantages of such long action potentially include increased patient compliance and minimisation of diurnal BP variation, thus providing greater protection against the development of major cardiovascular events and target organ damage.[8,42]

The fixed-dose combination of ramipril/felodipine ER administered once daily effectively reduces SBP and DBP in adults with essential hypertension with normal renal function whose hypertension is not controlled with monotherapy (section 3.1), or hypertensive patients with non-diabetic chronic renal disease (section 3.2). In this regard, fixed, low-dose combinations of ramipril/felodipine ER (i.e. 2.5mg/2.5mg and 5mg/5mg) once daily are more effective than individual components of the combination administered in equal doses in hypertensive patients with normal renal function (section 3.1.1). Likewise, the 5mg/5mg combination is more

effective in providing BP control than ramipril 10mg, and as effective as felodipine ER 10mg once daily in this patient population. Longer-term (12 months) satisfactory BP control can be expected in the majority of patients with essential hypertension receiving ramipril/felodipine ER either alone (up to 80%) or in combination with one or two other antihypertensive agents (up to 99% response rate) [section 3.1.2]. Data from a pilot study suggest that ramipril/felodipine ER fixed-dose combination may also be useful and safe for initiating the treatment of essential hypertension (section 3.1.1), but further confirmation is awaited from randomised, double-blind trials. In hypertensive patients with non-diabetic renal disease, the ramipril/felodipine ER 5mg/5mg fixed-dose combination seems more effective in achieving target BP than ramipril 10mg once daily (section 3.2.1). In the same patient population, once-daily treatment with the ramipril/felodipine ER combination appears to be as effective as double-dose ramipril, but more effective than felodipine ER 9mg once daily (mean dose) in slowing the progression of renal disease (section 3.2.2).

Hypertension treatment guidelines[4-7] indicate that more rigorous BP control (i.e. SBP/DBP 130/80mm Hg) is required in hypertensive patients with diabetes, and combination therapy is generally required to achieve this. Although there are currently no trials specifically evaluating the efficacy of ramipril/felodipine ER fixed-dose combination in hypertensive patients with diabetes (with or without renal disease), it may be expected that, in this patient population, ramipril/felodipine ER would be as effective in achieving BP control as other antihypertensive drug combinations.

When used at recommended dosages in clinical trials (section 5 and section 3), ramipril/felodipine ER fixed-dose combination was generally well tolerated in adult patients with essential hypertension (section 4). The most common adverse events associated with the combination were those related to individual components: headache, peripheral oedema and flushing with felodipine ER, and dry cough with ramipril, and were generally mild to moderate in severity. Using the ramipril/felodipine ER fixed-dose combination would be expected to reduce the incidence (section 4) and severity of certain adverse events associated with felodipine, such as peripheral oedema (figure 2), either through the compensatory activity of ramipril (i.e. venous dilation; section 2.1.1) or because of the lower dose of felodipine utilised in the combination than in monotherapy.

The success of antihypertensive therapy not only depends on the efficacy and tolerability of the therapeutic agent(s), but is also influenced by the costs of treatment and its effect on patients' well-being (i.e. health-related quality of life [HR-QOL]). Pharmacoeconomic and HR-QOL studies involving ramipril/felodipine ER fixed-dose combinations are not available at present. However, ramipril therapy has been previously reported in pharmacoeconomic models to be cost effective for the reduction of the risks of cardiovascular morbidity and mortality in hypertensive patients over treatment periods of up to 5[12,46,47] and 20 years (i.e. lifetime).[12] A retrospective analysis of pharmacy and medical claims databases from the US, including 125 000 patients with hypertension, indicated that the use of an ACE inhibitor and a dihydropyridine calcium channel antagonist in a fixed-dose combination could result in significant cost savings for both the patient and the healthcare provider.[48] In addition, an analysis of four randomised, double-blind clinical trials has shown that felodipine ER either as monotherapy or in combination with a β-blocker (metoprolol controlled-release) or an ACE inhibitor (ramipril, nifedipine sustained-release or diltiazem sustained-release) preserves the quality of life in hypertensive patients.[49] Importantly, this analysis also indicated an improvement in patients' well-being with the addition of ramipril to the therapy with felodipine ER;[49] however, confirmation of these findings would be required using the fixed-dose combination.

In conclusion, commercially available fixed-dose combinations (i.e. 2.5mg/2.5mg and 5mg/5mg) of ramipril and felodipine ER represent an effective and well tolerated therapy for adult patients with essential hypertension whose BP is inadequately controlled with monotherapy. In this patient popula-

tion, the ramipril/felodipine ER combinations are more effective at controlling hypertension than the individual components used as monotherapy at the same dosages. The 5mg/5mg combination is also as effective as felodipine ER 10mg, and more effective than ramipril 10mg administered as monotherapy. Furthermore, the addition of low-dose ramipril plus felodipine ER (fixed-dose or combination of individual components) to the existing antihypertensive regimen also appears to provide adequate BP control and renal protection in hypertensive patients with non-diabetic chronic renal disease. In these patients, the low-dose combination of ramipril and felodipine ER was as effective as standard-dose felodipine ER, but more effective than standard-dose ramipril, in reducing SBP and DBP, and as effective as standard-dose ramipril, but more effective than standard-dose felodipine ER, in slowing the rate of regression of glomerular filtration. The combination is as well tolerated as ramipril or felodipine ER monotherapy administered at the same dosages, and is better tolerated than felodipine ER monotherapy given at twice the dosage used in the combination (i.e. standard monotherapy dosage). Overall, ramipril/felodipine ER appears to be an effective option for the treatment of adults with essential hypertension that is poorly controlled by monotherapy. In addition, a fixed, low-dose combination of ramipril/felodipine ER may have further potential as an alternative to monotherapy for the initial management of essential hypertension.

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