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# Fixed-Dose Combination Enalapril/Nitrendipine

## A Review of its Use in Mild-to-Moderate Hypertension

*M. Asif A. Siddiqui* and *Greg L. Plosker*

Adis International Limited, Auckland, New Zealand

**Various sections of the manuscript reviewed by:**

***F. Antoñanzas***, Departamento de Economía y Empresa, Universidad de la Rioja, Logroño, Spain; ***A. de la Sierra***, Hypertension Unit, Department of Internal Medicine, Hospital Clínic, Barcelona, Spain; ***P.W. de Leeuw***, Department of Medicine, University Hospital, Universiteit Maastricht, Maastricht, The Netherlands; ***R. Fagard***, Hypertension and Cardiovascular Rehabilitation Unit, Katholieke Universiteit Leuven, Leuven, Belgium; ***G. Leonetti***, Istituto di Medicina Cardiovascolare, Università degli Studi di Milano, Milan, Italy; ***R. Marín***, Hospital de Covadonga, Oviedo, Spain; ***G.T. McInnes***, Division of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; ***A. Roca-Cusachs***, Department of Internal Medicine, Hospital de la Santa Creu i St Pau, Universitat Autonoma de Barcelona, Barcelona, Spain; ***J. Wang***, Hypertension and Cardiovascular Rehabilitation Unit, Katholieke Universiteit Leuven, Leuven, Belgium; ***J. Webster***, Department of Pharmacy, Grampian Health Board, Aberdeen, United Kingdom; ***A. Zanchetti***, Centro di Fisiologia Clinica e Ipertensione, Università degli Studi di Milano, Milan, Italy.

**Data Selection**

**Sources**: Medical literature published in any language since 1980 on enalapril/nitrendipine, 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 'enalapril nitrendipine' or 'enalapril' or 'nitrendipine'. EMBASE search terms were 'enalapril nitrendipine' or 'enalapril' or 'nitrendipine'. AdisBase search terms were 'enalapril nitrendipine' or 'enalapril' or 'nitrendipine'. Searches were last updated 20 April 2004.

**Selection**: Studies in patients with essential hypertension who received enalapril/nitrendipine. 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**: Enalapril/nitrendipine, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use, adverse events.

## Contents

## Summary

**Abstract**

The fixed-dose combination of enalapril 10mg with nitrendipine 20mg combines an ACE inhibitor with a calcium channel antagonist (CCA) and is indicated for the treatment of patients with mild-to-moderate hypertension whose blood pressure (BP) is inadequately controlled with enalapril or nitrendipine monotherapy. In randomised, double-blind clinical trials, enalapril/nitrendipine 10/20 mg/day was significantly more effective than its individual components in reducing diastolic BP (DBP) in patients with mild-to-moderate hypertension inadequately controlled with enalapril 10 mg/day or nitrendipine 20 mg/day. The fixed-dose combination was similar in efficacy at reducing DBP to amlodipine 10 mg/day in patients who failed to achieve BP control with amlodipine 5 mg/day, and to losartan/hydrochlorothiazide 50/12.5 mg/day in patients who received the combinations as first-line therapy. Enalapril/nitrendipine 10/20mg produced a consistent antihypertensive effect that persisted for the entire 24-hour dosage interval as shown by ambulatory BP monitoring.

Enalapril/nitrendipine 10/20mg was well tolerated in clinical trials where it was administered to patients with mild-to-moderate hypertension for up to 12 weeks. The adverse events were those expected of ACE inhibitors and CCAs and included cough, headache and flushing. Evidence from clinical trials, including a pooled analysis, suggests that the incidence of oedema may be significantly lower with the fixed-dose combination than with CCA monotherapy.

In conclusion, enalapril/nitrendipine 10/20mg is a well tolerated fixed-dose combination of two established antihypertensive agents administered once daily that effectively lowers BP throughout the 24-hour dosage interval. Importantly, the fixed-dose combination may have a lower incidence of oedema than CCA monotherapy. Enalapril/nitrendipine 10/20mg provides an additional treatment option for patients with mild-to-moderate hypertension for whom combination therapy is appropriate.

**Pharmacodynamic Properties**

Enalapril is an ACE inhibitor prodrug that is converted to the active moiety enalaprilat after absorption from the gastrointestinal tract. Nitrendipine is a dihydropyridine calcium channel antagonist (CCA).

In patients with hypertension, the single agents enalapril and nitrendipine as well as their combination effectively lower BP on a once-daily basis. Both have long-term beneficial effects on the cardiovascular system, improving left ventricular structure and function, with neutral and/or moderating effects on renal function, metabolic parameters and insulin sensitivity. Neither of these agents has any significant effect on electrolyte balance.

Enalapril/nitrendipine combination did not have any significant effect on heart rate (HR) in healthy volunteers.

 

## Pharmacokinetic Properties

There were no clinically relevant differences in the area under the plasma concentration-time curve and maximum plasma concentration values of enalapril or nitrendipine after single-dose administration of the fixed-dose combination enalapril/nitrendipine 10/20mg, compared with those observed with single agent enalapril 10mg or nitrendipine 20mg. There was no other pharmacokinetic interaction between the two drugs when coadministered.

## Therapeutic Efficacy

In two randomised, double-blind studies, patients with mild-to-moderate hypertension whose BP was not controlled with enalapril 10 mg/day or nitrendipine 20 mg/day monotherapies had significantly greater reductions in diastolic BP (DBP) with enalapril/nitrendipine 10/20 mg/day than those who continued on their respective monotherapies for 12 weeks. Pooled analysis of these two trials showed that the reduction in both systolic BP (SBP) and DBP with the combination therapy was significantly higher than that in patients receiving monotherapy (enalapril or nitrendipine). BP response rates were also significantly higher with enalapril/nitrendipine than those seen with the monotherapies in the pooled analysis, although one of the randomised trials did not show statistically significant differences between groups for SBP and DBP response rates.

After failure of amlodipine 5 mg/day to achieve BP control in patients with mild-to-moderate hypertension, enalapril/nitrendipine 10/20 mg/day was as effective as doubling the dosage of amlodipine in reducing DBP after 6 weeks. Although amlodipine 10 mg/day achieved significantly greater SBP reduction, there was no significant difference between the two treatments with respect to the proportions of patients achieving control of BP.

Enalapril/nitrendipine 10/20 mg/day was generally similar to a fixed-dose combination of losartan/hydrochlorothiazide (HCTZ) 50/12.5 mg/day in reducing BP in patients with mild-to-moderate hypertension as indicated by the reductions in office, 24-hour, daytime or night-time SBP/DBP measured by ambulatory BP monitoring (ABPM). Response rates were high and similar for both treatments. The only significant difference between the two treatments was with respect to office SBP control rates in favour of enalapril/nitrendipine.

The values of mean trough-to-peak ratios and the smoothness indices for the two treatments estimated during ABPM showed that the antihypertensive effects of both treatments persisted for the entire 24-hour dosage interval.

Pharmacoeconomic analyses of enalapril/nitrendipine therapy are limited to a modelled cost-effectiveness analysis conducted in Spain. Results indicated that enalapril/nitrendipine may provide a cost-effective treatment option in the treatment of hypertension.

## Tolerability

Enalapril/nitrendipine 10/20 mg/day was well tolerated in clinical trials, with the well known adverse effects of ACE inhibitors (e.g. cough) or CCAs (e.g. oedema, flushing and headache) being the most commonly reported adverse events.

The combination was at least as well tolerated as its individual components, and better tolerated than amlodipine 10 mg/day as shown by the incidence of adverse events considered to be at least possibly treatment-related, especially that of oedema. The incidence of oedema associated with enalapril/nitrendipine combination was two to three times lower than that observed with either nitrendipine 20 mg/day or amlodipine 10 mg/day. Adverse events observed with enalapril/

nitrendipine were generally similar in nature and incidence to those seen with losartan/HCTZ 50/12.5 mg/day.

Enalapril/nitrendipine had a neutral or a mild positive effect on the HR in clinical trials in patients with mild-to-moderate hypertension.

Adverse events were an infrequent cause of discontinuation of treatment with enalapril/nitrendipine in clinical trials. No deaths or serious adverse events related to study medication were reported in any of the trials.

## 1. Introduction

Essential hypertension is a heterogeneous disease involving several different blood pressure (BP) regulatory mechanisms wherein an imbalance in complex interactions results in an increase in BP. It is not surprising, therefore, that a single antihypertensive drug usually fails to achieve the desired BP control in patients with hypertension.[1,2] Moreover, counter-regulatory physiological mechanisms also tend to decrease the efficacy of antihypertensive drugs.[3] Consequently, the principle of polypharmacy in the treatment of hypertension has gained widespread acceptance.

ACE inhibitors and calcium channel antagonists (CCA) provide long-term beneficial effects on cardiovascular complications associated with high BP, in addition to their favourable efficacy/tolerability profiles.[3-6] When used in combination, renin release and reflex sympathetic activation caused by a CCA are counterbalanced, respectively, by antagonism of the renin-angiotensin system and modulation of sympathetic activity/responsiveness effected by ACE inhibition.[5,7,8]

This review focuses on the use of a fixed-dose combination of the ACE inhibitor enalapril and the CCA nitrendipine (enalapril/nitrendipine 10/20mg; Eneas®)[1] in the treatment of patients with mild-to-moderate essential hypertension. The individual drugs have been reviewed previously in *Drugs*.[9,10]

## 2. Pharmacodynamic Properties

Enalapril is an orally administered prodrug that is metabolised after absorption to form the active metabolite enalaprilat.[9,11] Enalaprilat exerts its antihypertensive effect by preventing the conversion of angiotensin I to the physiologically active vasocontrictor angiotensin II through inhibition of ACE.[9,11]

Nitrendipine is a dihydropyridine CCA that preferentially inhibits calcium influx through L-type channels of cardiac and vascular smooth muscle, thus inducing peripheral vasodilation with consequent reduction in BP.[10,12,13]

Table I provides an overview of the main pharmacodynamic properties of enalapril and nitrendipine. Specific studies assessing the pharmacodynamic properties of the enalapril/nitrendipine combination have not been performed. In a pharmacokinetic interaction study, enalapril/nitrendipine did not have any clinically significant effect on heart rate (HR) in healthy volunteers [32] (see also section 5).

## 3. Pharmacokinetic Properties

The pharmacokinetic properties of enalapril and nitrendipine are well known and have been reviewed previously in *Drugs*[9,10,33] and elsewhere.[11,13]

A pharmacokinetic interaction study using single oral doses of enalapril 20mg, nitrendipine 20mg or their combination indicated that there was no clinically significant pharmacokinetic interaction between the two drugs.[32] Subsequently, a randomised, crossover, single-dose study[34] compared the pharmacokinetics of enalapril/nitrendipine 10/20mg fixed-dose combination with those of enalapril 10mg and nitrendipine 20mg administered orally as single agents in 24 healthy volunteers. The pharmacokinetic parameters reported in this study are summarised in table II.

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

**Table I.** Overview of the pharmacodynamic properties of enalapril and nitrendipine in patients with essential hypertension

| Enalapril (enalaprilat)[a] | Nitrendipine |
|---|---|
| ACE inhibitor | Calcium channel antagonist |
| Effective in reducing both SBP and DBP for 24 hours;[9,11] efficacy does not diminish with continued treatment;[9] no rebound hypertension on withdrawal[9,11] | Lowers SBP and DBP and sustains this effect over 24 hours and during long-term administration[10,12,13] |
| Reduces PVR and increases CO with no significant change in HR[9,11] | Reduces PVR;[10,13] reflex tachycardia and consequent increase in CO seen after first few doses disappear with continued therapy[10,13] |
| Improves arterial compliance and diastolic function and reduces LV hypertrophy following long-term administration[9,11,14-16] | Improves aortic distensibility and/or LV hypertrophy/diastolic function, especially after long-term administration[17-20] |
| Improves effective RPF and decreases RVR; GFR is either unaffected or improved;[9,11] reduces microalbuminuria in diabetic patients[11,21-23] | Does not affect, or improves, GFR;[10,24-26] improves effective RPF and decreases RVR;[24] reduces microalbuminuria in diabetic patients[21,22,25,26] |
| Has no significant effects on electrolyte balance or metabolic parameters;[9,11] may improve lipid profile[9,11] and insulin sensitivity[27] | Has a short-lived natriuretic effect,[28,29] but does not significantly affect eletrolyte balance;[10,13] no adverse effects on glucose metabolism, insulin levels/sensitivity or lipid metabolism[30,31] |

a Enalapril is a prodrug that is metabolised to the ACE inhibitor enalaprilat.

**CO** = cardiac output; **DBP** = diastolic blood pressure; **GFR** = glomerular filtration rate; **HR** = heart rate; **LV** = left ventricular; **PVR** = peripheral vascular resistance; **RPF** = renal plasma flow; **RVR** = renal vascular resistance; **SBP** = systolic blood pressure.

The log transformed confidence intervals of the ratios of point estimates for the fixed-dose combination and single agent nitrendipine for maximum plasma concentration and area under the concentration-time curve of nitrendipine fell outside the acceptance interval of 80–125% generally required for showing bioequivalence[35] (table II).[34] However, these were not considered to be clinically relevant. All other pharmacokinetic parameters for both enalaprilat and nitrendipine following administration of the fixed-dose combination were similar to those obtained after administration of the respective single agents.[34]

## 4. Therapeutic Efficacy

The therapeutic efficacy of enalapril and nitrendipine as individual agents (previously reviewed in *Drugs*)[9,10,33] or in combination with each other[36-42] have been evaluated in a number of clinical trials. This section focuses on the antihypertensive efficacy of the fixed-dose combination enalapril/nitrendipine 10/20mg in comparison with enalapril or nitrendipine monotherapy (section 4.1),[36] amlodipine monotherapy (section 4.2)[39] or combination therapy with losartan/hydrochlorothiazide (HCTZ) [section 4.3][38,43] in patients with mild-to-moderate essential hypertension.

**Table II.** Comparative pharmacokinetics of the fixed-dose combination enalapril/nitrendipine (ENA/NIT) 10/20mg versus ENA or NIT administered orally as single agents in 24 healthy volunteers in a randomised, crossover, single-dose study.[34] All values are mean ± SD, except $t_{max}$ values which are given as medians

| Analyte | Treatment and dose (mg) | $C_{max}$ (ng/mL) | $AUC_\infty$ (ng • h/mL) | $C_{max}/AUC_\infty$ (per h) | $t_{max}$ (h) |
|---|---|---|---|---|---|
| Enalaprilat | ENA/NIT 10/20[a] | 49.63 ± 16.19 | 512.74 ± 105.80 | 0.096 ± 0.02 | 3.0 |
| | ENA 10 | 46.12 ± 20.64 | 504.98 ± 139.93 | 0.091 ± 0.03 | 4.0 |
| | 90% CI (%)[b] | 101.0–123.8 | 96.4–110.1 | 101.2–116.4 | 86.4–100 |
| Nitrendipine | ENA/NIT 10/20[a] | 9.19 ± 6.23 | 46.42 ± 59.10 | 0.259 ± 0.11 | 1.5 |
| | NIT 20 | 8.93 ± 11.78 | 42.52 ± 67.52 | 0.250 ± 0.11 | 1.8 |
| | 90% CI (%)[b] | 101.7–154.3 | 108.0–137.8 | 89.6–117.7 | 43.9–100.0 |

a Fixed-dose combination.

b Log transformed CI of ratio of point estimates.

**$AUC_\infty$** = area under the plasma concentration-time curve from time 0 to infinity; **CI** = confidence interval; **$C_{max}$** = maximum plasma concentration; **$t_{max}$** = time to reach $C_{max}$.

**Table III.** Efficacy of the fixed-dose combination enalapril/nitrendipine (ENA/NIT) 10/20mg in comparison with ENA or NIT monotherapies in patients (pts) with essential hypertension in 12-week, randomised, double-blind, parallel group, multicentre trials (available as a poster)[36]

| Trial | Pre-randomisation active run-in[a] | Treatment regimen (mg/day)[b] | No. of pts[c] | Mean baseline SBP/DBP (mm Hg)[d] | Mean ↓ in SBP/DBP from baseline (mm Hg) | Responders (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | SBP/DBP[e] | SBP[f] | DBP[g] |
| ENEAS-1 | ENA 10mg × 6 wks | ENA/NIT 10/20 | 117 | 151.9/95.4 | 10.7/7.7** | 56* | 52* | 70** |
| | | ENA 10 | 125 | 152.7/96.2 | 9.2/6.0 | 43 | 39 | 54 |
| ENEAS-2 | NIT 20mg × 6 wks | ENA/NIT 10/20 | 100 | 152.3/95.1 | 10.1/7.6* | 52* | 45 | 58 |
| | | NIT 20 | 122 | 154.0/95.7 | 9.0/5.7 | 39 | 36 | 47 |

a Pts not responding (DBP ≥90mm Hg) to monotherapy advanced to the randomised phase.

b All agents were administered orally once daily for 12 wks.

c Per-protocol population.[34]

d At randomisation to the double-blind phase.

e <140/90mm Hg or ↓ by ≥20/10mm Hg.

f <140mm Hg or ↓ by ≥20mm Hg.

g <90mm Hg or ↓ by ≥10mm Hg.

**DBP** = diastolic blood pressure; **ENEAS** = European Nitrendipine and Enalapril Association Study; **SBP** = systolic blood pressure; **wks** = weeks; ↓ indicates decrease; * $p < 0.05$, ** $p \leq 0.01$ vs comparator.

As mentioned in section 2, enalapril and nitrendipine are well established antihypertensive agents with complementary mechanisms. A 6-week dose-finding study established the optimal dosage regimen for the drugs when used concomitantly, and the fixed-dose combination of enalapril/nitrendipine 10/20mg was developed on the basis of these results.[44] In this randomised, double-blind, placebo-controlled trial, all 16 possible combinations of enalapril (0, 5, 10 and 20mg) and nitrendipine (0, 5, 10 and 20mg) were evaluated in a total of 342 patients with mild-to-moderate hypertension. Enalapril/nitrendipine combination therapy yielded an additive antihypertensive effect at the end of the dosage interval, significantly greater than that of monotherapy with its individual components ($p < 0.01$). The combination of enalapril 10mg plus nitrendipine 20mg once daily resulted in the maximum reduction from baseline in sitting diastolic BP (DBP) [−14.3mm Hg], with a reduction of −16.9mm Hg in sitting systolic BP (SBP).[44]

Subsequent clinical trials of the fixed-dose combination enalapril/nitrendipine 10/20mg were all randomised, controlled studies of 4–18 weeks duration (see tables III and IV for details),[36,38,39] although only one is fully published.[38] A double-dummy technique was employed, where required, to ensure blinding. Patients with stage I or II hypertension[45] with DBP 90–109mm Hg (95–109mm Hg in patients not under treatment in one trial)[38] received placebo for 2–3 weeks before starting on active treatment. In three studies,[36,39] inclusion criteria required that patients had inadequate BP control (DBP ≥90mm Hg) after an active run-in with antihypertensive monotherapy before randomisation into the double-blind period. BP measurements were generally performed in a sitting position, with office BP measured at trough plasma drug levels (22–24 hours after drug administration).[34,38] Exclusion criteria included stage III,[45] secondary or malignant hypertension, New York Heart Association class III or IV heart failure, arrhythmia, coronary disease or stroke within the last 6 months, chronic kidney or liver failure or uncontrolled diabetes mellitus.

Mean reduction from baseline in DBP was generally regarded as the primary endpoint, although reductions in SBP were also reported. Control of BP was defined as office SBP and/or DBP <140/90mm Hg[38,39] (or daytime SBP and/or DBP <130/85),[38] while reduction in office SBP by ≥20 or DBP by ≥10mm Hg (or 24-hour SBP by ≥10 or DBP by ≥5mm Hg) was considered response to treatment.[38] However, in the European Nitrendipine and Enalapril Association Studies (ENEAS-1 and -2)[36] response was not differentiated from BP control (section 4.1).

The only trial that employed ambulatory BP monitoring (ABPM) also reported trough-to-peak ratios (T/P ratio = ratio of average BP reduction at peak to that at trough) and smoothness indices (SI = average hourly BP change divided by its standard deviation) of the combinations compared.[38]

### 4.1 Comparisons with Enalapril or Nitrendipine Monotherapy

In patients with hypertension not controlled by enalapril 10 mg/day (ENEAS-1) or nitrendipine 20 mg/day (ENEAS-2), enalapril/nitrendipine 10/20 mg/day was significantly more effective than either monotherapy in reducing DBP from baseline at the end of 12 weeks (table III).[36] The reductions from baseline in SBP in patients receiving the fixed-dose combination were not statistically different from those in monotherapy recipients in either trial.[36]

Depending on the criteria used to define response, response rates ranged from 45% to 70% with the fixed-dose combination compared with 39–54% with enalapril and 36–47% with nitrendipine. The porportions of responders were numerically higher with the combination than with either of the monotherapies, the difference reaching statistical significance versus enalapril monotherapy for all comparisons and versus nitrendipine monotherapy for a global definition of response (table III).[36]

In a pooled analysis of the two trials,[46] enalapril/nitrendipine reduced SBP/DBP by 10.9/8.3mm Hg compared with a reduction of 8.6/5.9mm Hg observed in patients receiving monotherapy (enalapril 10 mg/day or nitrendipine 20 mg/day). The difference was statistically significant for both SBP ($p = 0.044$) and DBP ($p = 0.001$). Compared with monotherapy, treatment with enalapril/nitrendipine was associated with significantly greater systolic (38% vs 49%; $p = 0.015$) or diastolic (50% vs 65%; $p = 0.002$) response rates.[46] The proportion of patients showing both systolic and diastolic (global) response was also greater with enalapril/nitrendipine (54%) than with monotherapy (41%; $p = 0.004$).[46]

### 4.2 Comparison with Dose-Titrating Amlodipine Monotherapy

In patients with mild-to-moderate hypertension whose BP was not adequately controlled on amlodipine 5 mg/day, enalapril/nitrendipine 10/20 mg/day was as effective as increasing amlodipine dosage to 10 mg/day at reducing DBP after 6 weeks of therapy (table IV).[39] Amlodipine 10 mg/day reduced SBP to a significantly greater extent than enalapril/nitrendipine.[39]

Control of BP was achieved in 55–75% or 60–80% of patients receiving enalapril/nitrendipine or amlodipine, with no significant difference between the two treatments (table IV).[39]

### 4.3 Comparison with Losartan/Hydrochlorothiazide Combination Therapy

Enalapril/nitrendipine 10/20 mg/day and losartan/HCTZ 50/12.5 mg/day, administered as first-

**Table IV.** Efficacy of the fixed-dose combination enalapril/nitrendipine (ENA/NIT) 10/20mg in comparison with amlodipine (AML) or losartan/hydrochlorothiazide (LOS/HCTZ) in patients (pts) with essential hypertension in randomised, double-blind, parallel group, multicentre trials

| Study | Treatment regimen (mg/day)[a] | No. of pts[b] | Mean baseline SBP/DBP (mm Hg)[c] | Mean ↓ in SBP/DBP from baseline (mm Hg) | Pts achieving BP control (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | SBP/DBP <140/90mm Hg | SBP <140mm Hg | DBP <90mm Hg |
| Marin et al.[39][d] | ENA/NIT 10/20 | 100 | 149.8/94.9 | 8.2/7.7 | 55 | 60 | 75 |
| | AML 10 | 98 | 153.4/94.8 | 12.1**/9.2 | 60 | 70 | 80 |
| de la Sierra et al.[38] | ENA/NIT 10/20 | 45 | 161.9/100.2 | 21.0/12.1 | 33 | 42* | 53 |
| | LOS/HCTZ 50/12.5 | 49 | 164.4/101.1 | 19.4/10.9 | 20 | 22 | 39 |

a All agents were administered orally once daily for 6[39] or 4[38] wks.

b Per-protocol[39] or intention-to-treat[38] population.

c At randomisation to the double-blind phase.

d Pts not responding (DBP ≥90mm Hg) to monotherapy with AML 5mg for 4 wks advanced to the randomised phase.

**DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; **wks** = weeks; ↓ indicates decrease; * $p = 0.048$, ** $p = 0.017$ vs comparator.

line therapy, had similar overall efficacy in reducing BP in patients with mild-to-moderate hypertension (table IV and figure 1).[38] The reductions in 24-hour DBP (main efficacy variable monitored using ABPM) showed no significant difference between the fixed combinations after 4 weeks' treatment (figure 1). Furthermore, reductions in 24-hour SBP, and office, daytime and night-time SBP/DBP were also similar between treatment groups.[38]

The 24-hour and office BP control rates with enalapril/nitrendipine tended to be higher than with losartan/HCTZ, but only the difference between office SBP control rates reached statistical significance (table IV). Response rates (as defined earlier in this section) were approximately 60% or higher with both treatments, with no significant beween-group differences.[38]

Trough-to-peak ratios (>0.5) and smoothness indices (>1) for both groups indicated that each treatment provided a relatively consistent BP-lowering effect throughout the dosage interval.[38] Importantly, a high degree of patient compliance (~99%) to both treatments was reported in this trial.[43]

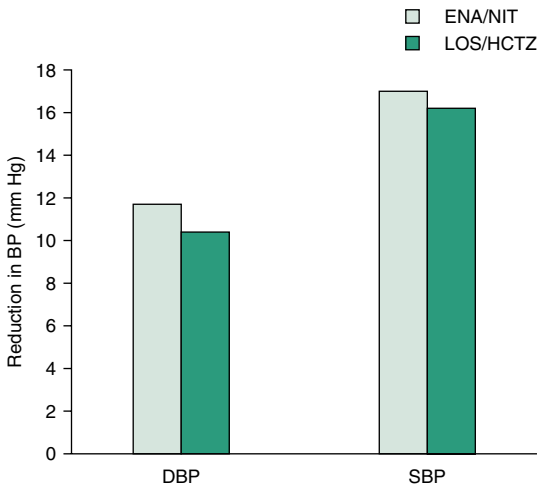


**Fig. 1.** Comparative efficacy of fixed combinations enalapril/nitrendipine (ENA/NIT) 10/20 mg/day and losartan/hydrochlorothiazide (LOS/HCTZ) 50/12.5 mg/day. The reductions in 24-hour diastolic blood pressure (DBP) [primary efficacy variable] and systolic BP (SBP) in patients with mild-to-moderate hypertension randomised to receive ENA/NIT (n = 45) or LOS/HCTZ (n = 49) for 4 weeks in a double-blind, parallel-group trial.[38] Ambulatory BP monitoring was performed to assess the response to treatment. The baseline 24-hour SBP/DBP values in the two groups were (mm Hg): ENA/NIT, 145.1/90.0; LOS/HCTZ, 145.4/90.5.

## 5. Tolerability

The tolerability profiles of enalapril[9] and nitrendipine[10] in patients with hypertension are well established and have been previously reviewed in detail. This section reviews the tolerability data obtained in clinical trials of the fixed-dose combination enalapril/nitrendipine 10/20mg (section 4) supplemented, where required, by the results of the dose-finding study.[44]

Enalapril/nitrendipine was well tolerated in patients with mild-to-moderate hypertension in clinical trials in which it was administered once daily for up to 12 weeks.[34,36,38,39] The most commonly reported adverse events with the fixed-dose combination were the well known adverse effects of ACE inhibitors (e.g. cough) or CCAs (e.g. oedema, flushing, headache).[34,36,38,39] There was no indication of an additive effect of enalapril and nitrendipine in causing the adverse effects when coadministered.[44]

In general, the incidence of adverse events reported with enalapril/nitrendipine was comparable to that with enalapril 10 mg/day or nitrendipine 20 mg/day, when events possibly attributable to the study drugs were considered in ENEAS trials (section 4.1).[34] For example, cough was reported in similar proportions of patients in the fixed-dose combination (5.1%) and enalapril (4.9%) groups in ENEAS-1.[34,36] Notably, however, the incidence of oedema was >2-fold higher in patients receiving nitrendipine (9%) than that in enalapril/nitrendipine recipients (3.6%) in ENEAS-2.[34]

The overall incidence of adverse events considered at least possibly treatment-related with enalapril/nitrendipine was significantly lower than that reported in patients receiving amlodipine 10 mg/day (19.8% vs 37.0%; p = 0.003) [section 4.2][39] and numerically higher than that in recipients of losartan/HCTZ 50/12.5 mg/day (27.1% vs 14.3%) [section 4.3].[38]

In the trial comparing enalapril/nitrendipine with amlodipine 10 mg/day for 6 weeks, all adverse events, with the exception of oedema, were reported

in <5% of patients in either group.[34] In this study, all patients were given amlodipine 5 mg/day for 4 weeks to identify non-responders (section 4.2); thus, any patients with poor tolerability to CCA therapy would have discontinued before randomisation. This may, at least partially, explain the low overall incidence of reported adverse events. In the ABPM study comparing enalapril/nitrendipine and losartan/HCTZ, headache (10.4% vs 0%), gastrointestinal disorders (8.3% vs 2.0%), flushing (8.3% vs 0%) and dizziness (2.1% vs 8.2%) were the most frequent adverse events (incidence >5%) [statistical significance not reported].[38]

The incidence of ankle oedema was three times lower in the enalapril/nitrendipine group than that in amlodipine group (11.1% vs 33.6%; $p < 0.0001$).[39] In a pooled analysis of five randomised, double-blind studies, the incidence of oedema was significantly lower in patients receiving enalapril/nitrendipine than in recipients of alternative treatment options (6.0% vs 9.3%; $p < 0.0001$).[47] The comparator group for this analysis comprised data from patients receiving enalapril,[36] nitrendipine,[36] amlodipine,[39] losartan/HCTZ[38] and enalapril/HCTZ (unpublished). This overall difference was mainly attributed to the sizable difference between the incidence of oedema associated with dihydropyridine CCA monotherapy (nitrendipine or amlodipine) and the CCA/ACE inhibitor fixed-dose combination.[47]

Discontinuation of treatment due to adverse events was infrequent during clinical trials; the discontinuation rate with enalapril/nitrendipine was 6% in each of the two trials[34,38] compared with 0% in losartan/HCTZ[38] and 3% in amlodipine[34] recipients. No deaths or serious adverse events related to study medication were reported in any of the trials.[34,38]

Enalapril/nitrendipine generally had a neutral[43] or a mild positive[36,39] effect on HR. In patients switching from amlodipine 5 mg/day, there was a significant reduction in HR at the end of study in enalapril/nitrendipine recipients, compared with that in patients for whom dosages were increased to amlodipine 10 mg/day (difference of −2.2 beats per minute; $p < 0.01$).[39]

Routine laboratory safety parameters did not show any clinically significant abnormalities with enalapril/nitrendipine.[36,38]

## 6. Dosage and Administration

The information on dosage recommendations is mainly based on the prescribing information of the fixed-dose combination enalapril/nitrendipine 10/20mg.[48]

The fixed-dose combination enalapril/nitrendipine 10/20mg is indicated for the treatment of patients with mild-to-moderate essential hypertension whose BP is not adequately controlled on enalapril or nitrendipine monotherapy. The recommended dosage in adults (including elderly patients) is one tablet of fixed-dose combination enalapril/nitrendipine 10/20mg daily. As appropriate, dose titration with individual components or direct switch from monotherapy to the fixed-dose combination may be recommended.[48]

Enalapril/nitrendipine is contraindicated in patients with severe hepatic or severe renal impairment including those on haemodialysis.[48] Although enalapril or nitrendipine monotherapy is not contraindicated in patients with mild-to-moderate impairment of hepatic or renal function, caution should be exercised when the combination is administered to these patients. Patient monitoring, especially that of the impaired renal function, is recommended.[48]

Enalapril/nitrendipine is also contraindicated in children, adolescents and pregnant or breast-feeding women. In general, the fixed-dose combination should not be administered to patients in whom an ACE inhibitor or a CCA is contraindicated.[48]

No specific drug interaction studies have been performed with the enalapril/nitrendipine combination (see also section 3). As expected, the antihypertensive effect of the combination may be enhanced by concomitant administration of other antihypertensive agents. Full details of the drug interactions of enalapril and nitrendipine administered as individual agents may be found elsewhere.[10,48-51]

## 7. Place of Enalapril/Nitrendipine in the Management of Mild-to-Moderate Hypertension

Hypertension, which affects approximately one billion individuals worldwide,[52] is a major risk factor for myocardial infarction, heart failure, stroke and kidney disease.[52-55] According to a WHO estimate,[56] high BP was the third leading cause of mortality in the world, responsible for one in every eight deaths. Thus, hypertension and its associated conditions impose a tremendous burden on healthcare resources and also have profound social implications.[52,54] Given the enormity of the problem, effective management of hypertension is a major healthcare challenge in most countries.

Despite slight differences in their recommended BP targets (table V), all major hypertension guidelines take the patient's risk category into consideration while emphasising the reduction in the risk of cardiovascular mortality and morbidity associated with high BP as an important treatment objective.[52-55] In recognition of this association and the fact that 30% of patients are unaware that they have hypertension,[52] the approach towards treatment of hypertension has become more aggressive in recent years.

In the majority of patients with hypertension, nonpharmacological approaches serve only as useful adjuncts to drug treatment, which is required to maintain adequate BP control. Together with ACE inhibitors and CCAs, there are five major classes of drugs (diuretics, β-adrenoceptor antagonists and angiotensin II receptor antagonists being the others) used in the treatment of hypertension. While JNC-VII (seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) guidelines[52] recommend the use of diuretics as first-line therapy, the other guidelines[53-55] are unanimous that treatment can be initiated and maintained with any class of drugs, unless there is a compelling indication/contraindication for a particular class. Irrespective of which class is chosen, all four guidelines[52-55] generally recommend a stepwise approach: treatment initiation with a single agent at a low dosage and, if BP reduction is suboptimal, dosage increase, change of drug or use of combination therapy.

**Table V.** Blood pressure (BP) goals recommended in various guidelines on the management of hypertension

| Guideline | BP goals in adult patients (SBP/DBP [mm Hg]) | |
|---|---|---|
| | without diabetes | with concomitant diabetes |
| ESH-ESC[53] | <140/90 | <130/80 |
| BHS[54] | <140/85 | <130/80 |
| WHO-ISH[55] | <130/85[a] | <130/85[a] |
| JNC-VII[52] | <140/90 | <130/80 |

a For adult patients with or without diabetes; the goal for the elderly is <140/90mm Hg.

**BHS** = British Hypertension Society; **DBP** = diastolic BP; **ESH-ESC** = European Society of Hypertension – European Society of Cardiology; **JNC-VII** = the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP; **SBP** = systolic BP; **WHO-ISH** = World Health Organization – International Society of Hypertension.

A high proportion of patients (~50–70%) starting on antihypertensive monotherapy discontinue or change their medication due to adverse effects, lack of efficacy or cost.[57,58] Indeed, as acknowledged in the guidelines,[52-55] adequate BP control is often difficult to achieve with monotherapy and most patients with hypertension will require a combination of antihypertensive agents to achieve optimal control. Accordingly, after careful consideration of the baseline BP and presence/absence of complications, therapy may be initiated with a low-dose combination of two agents.[52,53]

Among the proposed benefits of combination therapy over high-dose monotherapy are a lower incidence of adverse effects and better efficacy.[5,6,8,59-61] The individual agents used in combination generally have established efficacy and tolerability profiles, and their optimal dosages have already been identified.[60] Furthermore, one of the reasons for the failure of antihypertensive therapy is poor patient compliance,[62] which may be worsened by the prevalence of polypharmacy in patients with hypertension. Given that patient compliance is correlated with the daily number of medications the patient is required to take,[63] the use of a fixed-dose combination provided in a single formulation may improve patient compliance[60] and, thus, BP control. Patient compliance is also improved by simpli-

fying treatment regimens with the use of long-acting antihypertensive agents that minimise BP variation to achieve a smooth 24-hour BP control on a once-daily basis.[53,64] Lastly, fixed-dose combinations offer the advantage of generally lower costs than those associated with extemporaneous combinations.[60]

The issue of the lack of dose administration flexibility has been frequently raised as a potential disadvantage of fixed-dose combinations.[60] However, in contrast to clinical trials where drug therapy is often titrated to achieve target BP goals, it is rare for the physicians to titrate or modify BP therapy in clinical practice.[65] Also, given that compliance is inversely related to the complexity of the dose administration regimen,[60] this advantage of coadministering individual drugs may be counterproductive.

A plethora of fixed-dose combinations have been approved worldwide for the treatment of patients with hypertension over the past two decades, with the majority containing a diuretic. More recently, however, fixed-dose combinations of CCAs with ACE inhibitors have become commercially available.

The utility of combined therapy with enalapril and nitrendipine in the treatment of patients with hypertension was highlighted by the Systolic Hypertension in Europe (Syst-Eur) study[41] and a subsequent dose-finding study identified enalapril 10mg plus nitrendipine 20mg as the dosage combination providing optimal BP control.[44] Subsequent clinical studies (ENEAS-1 and -2) have demonstrated that the fixed-dose combination of enalapril/nitrendipine 10/20mg provides significant improvement in BP control compared to monotherapy treatment with either of the individual constituents in patients with mild-to-moderate hypertension (section 4.1). Enalapril/nitrendipine also conferred similar BP control to amlodipine 10 mg/day (section 4.2) and the fixed combination of losartan/HCTZ 50/12.5 mg/day (section 4.3).

The mean T/P ratio (>0.5) and the SI (>1) obtained during ABPM (section 4.3) showed that enalapril/nitrendipine provided a consistent antihypertensive effect over the 24-hour dosage interval. This minimises BP variability and may lead to a greater protection against cardiovascular events or the development of target-organ damage.[64] Furthermore, compliance with enalapril/nitrendipine therapy was reported to be excellent in this well designed, albeit short-term, clinical trial (section 4.3), although details of the method of measurement of compliance were not provided.

The fixed-dose combination was at least as well tolerated as monotherapy with enalapril 10 mg/day, amlodipine 10 mg/day or nitrendipine 20 mg/day, or another fixed-dose combination (losartan/HCTZ 50/12.5 mg/day) in randomised, double-blind clinical trials (section 5). Of note, while cough occurred with similar frequency in enalapril/nitrendipine 10/20 mg/day or enalapril 10 mg/day recipients, the incidence of oedema was significantly lower with the combination than that in patients treated with CCA monotherapy (amlodipine 10 mg/day or nitrendipine 20 mg/day) [section 5]. Further confirmation of this lowered incidence of oedema with the fixed-dose combination is required from larger well designed studies of longer duration.

Although enalapril/nitrendipine 10/20 mg/day successfully lowered BP when administered for 4–12 weeks (section 4), to date there are no studies evaluating effects of long-term treatment with the fixed-dose combination on morbidity and mortality. Given the favourable cardiovascular effects of enalapril and nitrendipine monotherapies after long-term administration (section 2) and some evidence from the Syst-Eur trial[41] it is anticipated that this combination may have long-term beneficial effects in preventing complications associated with hypertension.

The fixed-dose combination has shown efficacy as first-line therapy in the treatment of a limited number of patients with mild-to-moderate hypertension (section 4.3). As mentioned earlier in this section, hypertension guidelines recommend use of a combination as first-line therapy only after careful risk/benefit assessment. A recent meta-analysis has also shown that combination therapy is more effective as first-line treatment than monotherapy in reducing BP with no associated increase in adverse events.[66] However, more studies comparing

enalapril/nitrendipine with other antihypertensive combinations would be valuable in determining with greater certainty the place of this combination in the management of patients with hypertension.

Pharmacoeconomic data on enalapril/nitrendipine are limited. A modelled cost-effectiveness study from Spain has suggested that in patients with mild-to-moderate hypertension who failed monotherapy treatment with enalapril or nitrendipine, switching to enalapril/nitrendipine fixed combination may be a more cost-effective option than increasing the dosage of current monotherapy or switching to another treatment.[67] However, further robust prospective pharmacoeconomic studies are required to confirm these initial observations.

In conclusion, enalapril/nitrendipine 10/20mg is a well tolerated fixed-dose combination of two established antihypertensive agents that effectively lowers BP throughout the dosage interval after once-daily administration. Enalapril/nitrendipine fixed-dose combination offers a convenient and effective means of improving BP control in patients whose BP is inadequately controlled by either agent alone. For patients not responding to low-dose CCA monotherapy, the fixed-dose combination may be a useful alternative to an increase in CCA dosage. Importantly, enalapril/nitrendipine may have a lower incidence of oedema than CCA monotherapy. Enalapril/nitrendipine fixed combination provides an additional treatment option for patients for whom combination therapy is appropriate.

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Correspondence: *M. Asif A. Siddiqui*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz