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Delapril/Manidipine

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Contents

Abstract

▲ Delapril/manidipine 30mg/10mg is a new oral, once-daily, fixed combination of an ACE inhibitor and a dihydropyridine calcium-channel antagonist for the treatment of essential hypertension.

▲ In a dose-finding study in 400 patients with mild to moderate hypertension, delapril/manidipine 30mg/10mg once daily produced the greatest reduction in blood pressure (BP) of the combinations tested. Delapril/manidipine 30mg/10mg once daily for 6 weeks reduced systolic BP (SBP)/diastolic BP (DBP) by 15/13mm Hg.

▲ In nonresponders to monotherapy with delapril (n = 155) or manidipine (n = 152), delapril/manidipine 30mg/10mg once daily for 12 weeks reduced mean SBP/DBP by 16/11mm Hg and 16/10mm Hg, respectively.

▲ Delapril/manidipine 30mg/10mg once daily for 12 weeks in patients with mild to moderate hypertension (n = 131) demonstrated significantly greater antihypertensive efficacy than monotherapy with manidipine 10mg once daily (n = 134) or delapril 15mg twice daily (n = 136). Mean SBP/DBP reductions from baseline were 19/14, 15/11 and 14/10mm Hg, respectively.

▲ After 50 weeks of therapy with delapril/manidipine 30mg/10mg once daily, mean SBP/DBP was reduced by 22/14mm Hg in patients with mild to moderate hypertension (n = 309).

▲ Delapril/manidipine 30mg/10mg once daily was generally well tolerated. The incidence and nature of adverse events were similar to those observed in recipients of monotherapy with the individual agents. Combination therapy was associated with less ankle oedema than manidipine monotherapy.

Features and properties of delapril/manidipine fixed combination tablet (CHF 1521; VIVACE®)	
Indication	
Essential hypertension in adults	
Mechanisms of action	
ACE inhibition (delapril); L-type calcium channel antagonism (manidipine)	
Dosage and administration	
Dosage	Delapril 30mg; manidipine 10mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (single dose of delapril/manidipine 30mg/10mg fixed combination tablet [unless stated otherwise] in healthy volunteers)	
Peak plasma concentration (ng/mL)	365 (delapril diacid metabolite [M1]); 173 (delapril 5-hydroxy diacid metabolite [M3]); 177 (delapril); 3.27 (manidipine)
Time to peak plasma concentration (h)	1.5 (M1); 2.0 (M3); 1.0 (delapril); 1.75 (manidipine)
Area under the plasma concentration-time curve (ng • h/mL)	928 (M1); 528 (M3); 215 (delapril); 13.2 (manidipine)
Elimination half-life (h) [components separately coadministered]	1.60 (M1); 1.29 (M3); 0.44 (delapril); 3.29 (manidipine)
Adverse events	
Most common	Cough, oedema and headache

Hypertension affects approximately 1000 million individuals worldwide,[1] and is associated with an increased risk of cardiovascular morbidity and mortality and with end-stage renal disease.[1,2] There is virtually a continuous relationship between the level of blood pressure (BP) and cardiovascular risk, such that the greater the reduction in BP achieved, the greater the benefits.[2]

Despite the well recognised need to lower BP in patients with hypertension, only about half of all treated patients achieve BP control (systolic BP [SBP] <140mm Hg and diastolic BP [DBP] <90mm Hg).[1] Most patients will require two or more antihypertensive medications to achieve the required BP goals.[1] The major guidelines for the management of hypertension[1-3] all recommend the use of combination therapy with low doses of agents from different antihypertensive classes, rather than further increasing the dosage of the initial agent, when initial therapy does not achieve the BP goal after titration to the usual maintenance dosage.

The advantages of combination therapy are a greater likelihood of controlling BP and its complications by using drugs with different and complementary mechanisms of action; the ability to use low doses of agents that are more likely to be free of adverse effects; and the belief that administration of fixed combinations of different agents in a single tablet is likely to increase patient compliance, especially when long-acting agents requiring once-daily administration are used.[2]

Calcium antagonists and ACE inhibitors are well established as effective agents for the treatment of essential hypertension and have been shown to be effective and well tolerated when used in combination.[2,4,5]

This profile focuses on a new oral, once-daily, fixed combination of the ACE inhibitor delapril (30mg) and the dihydropyridine calcium antagonist manidipine (10mg) [VIVACE®][1] in the treatment of adult patients with essential hypertension.

1. Pharmacodynamic Profile

The delapril/manidipine fixed combination tablet combines two antihypertensive drugs with distinctly different mechanisms of action that have additive or complementary pharmacodynamic effects. The pharmacodynamic properties of manidipine and delapril have been well characterised (see reviews on delapril[6,7] and manidipine[8]), and only the key properties are summarised in this section.

Delapril

- Delapril is a nonsulfhydryl, lipophilic ACE inhibitor.[6,7] It is an ester prodrug that is metabolised to an active diacid metabolite (M1), which in turn is metabolised to an active 5-hydroxy diacid derivative (M3) and an inactive metabolite (M2).[6,7]
- The antihypertensive action of delapril is maintained for up to 24 hours owing to long-lasting ACE inhibition, despite the relatively short plasma half-lives of its active derivatives (section 2).[9] Delapril has renoprotective and cardioprotective properties, and a lower propensity than captopril or enalapril to cause cough.[6,7]

Manidipine

- Manidipine is a dihydropyridine L-type calcium channel antagonist with a slow onset of action, which minimises reflex tachycardia, and a long duration of effect.[8,10] Manidipine has little cardiodepressant activity, is metabolically neutral and displays renoprotective, natriuretic and diuretic effects.[8]

Delapril/Manidipine

- Delapril/manidipine combination therapy improves fibrinolytic function, which may be impaired in patients with hypertension and type 2 diabetes mellitus.[11] In a randomised, double-blind study in adult hypertensive patients with type 2 diabetes (n = 76), delapril 30mg monotherapy for 8 weeks significantly ($p < 0.05$ vs baseline) decreased the plasma levels of plasminogen activator inhibitor-1 (PAI-1),

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

and the addition of manidipine 10mg for another 8 weeks significantly ($p < 0.05$) increased the levels of tissue plasminogen activator (t-PA), thereby improving the PAI-1 : t-PA ratio (20 vs 52 at baseline).[11]

- In contrast, irbesartan 150mg once daily for 8 weeks followed by irbesartan/hydrochlorothiazide (HCTZ) 150mg/12.5mg once daily for 8 weeks worsened the PAI-1 : t-PA ratio (89 vs 56 at baseline).[11]
- In patients with uncontrolled hypertension and type 2 diabetes (n = 189), serum creatinine levels were significantly ($p < 0.01$) increased from baseline after treatment for 50 weeks with ramipril/HCTZ 2.5mg/12.5mg once daily (4.91 μmol/L) or valsartan/HCTZ 80mg/12.5mg once daily (4.32 μmol/L), but not with delapril/manidipine 30mg/10mg once daily (1.65 μmol/L), suggesting a renoprotective action for delapril/manidipine (published as an abstract).[12]
- Of patients with proteinuria at baseline in this study, 43% had normal urinary protein levels after treatment with delapril/manidipine compared with 20% and 36% of those treated with ramipril/HCTZ and valsartan/HCTZ, respectively.[12]

2. Pharmacokinetic Profile

The pharmacokinetic properties of delapril[6,13-16] and manidipine[8,17-19] have each been well characterised and the pharmacokinetic properties of the delapril/manidipine combination have been assessed in young adult and elderly healthy volunteers.[20,21]

Delapril

- Delapril is rapidly absorbed following oral administration, with times to reach peak plasma concentration (t_{max}) for delapril, M1 and M3 of approximately 1.0–1.1, 1.2–1.4 and 1.7–1.9 hours, respectively.[6,13-16] The peak plasma concentration (C_{max}) values for M1 are approximately 2.5-fold higher than those of M3 and 5-fold higher than those of the parent drug.[13]
- Elimination is relatively rapid; the elimination half-life ($t_{1/2}$) values for delapril, M1 and M3 being approximately 0.5, 1.2 and 0.8 hours, respectively.[13] Approximately 56% of the administered dose is excreted in the urine, mainly as M1 (21%) and M3 (30%).[6,13]
- In patients with renal impairment, the area under the plasma concentration-time curve (AUC), C_{max} and $t_{1/2}$ of the active metabolites are increased, indicating a need for dosage adjustment in patients with marked renal impairment.[6,13,14]

Manidipine

- Manidipine t_{max} after an oral dose is ≈1.5 hours.[8] Administration with food increases the AUC by about 40% and C_{max} by approximately 20%.
- Manidipine undergoes extensive first-pass hepatic metabolism to a number of pharmacologically inactive derivatives.[17,18] The bulk of the dose (63%) is eliminated in the faeces.[17] The $t_{1/2}$ of manidipine appears to vary with the dose, but is in the range of 4–5 hours for a single 10 or 20mg dose.[8,19]
- The bioavailability of manidipine is increased, as a result of delayed elimination, in patients with more severe hepatic dysfunction.[19]

Delapril/Manidipine

- Coadministration of single oral doses of delapril 30mg and manidipine 10mg in healthy male volunteers (n = 18) did not significantly alter the pharmacokinetics of either drug or those of their major metabolites.[20]
- After single-dose administration in young adult volunteers, strict bioequivalence was demonstrated between the fixed combination tablet and the components separately coadministered.[21] Following single-dose administration of the fixed combination, pharmacokinetic values for delapril were C_{max} 177 ng/mL, t_{max} 1.0h and AUC_{∞} 215 ng • h/mL, while those for manidipine were C_{max} 3.27 ng/mL, t_{max} 1.75h and AUC_{∞} 13.2 ng • h/mL.[21] There was no

significant accumulation after repeated dose administration once daily for 1 week.[21]

- Likewise, there was no significant accumulation during repeated dosing in elderly volunteers (aged 65–75 years).[21]
- Drug exposure was higher in elderly than in young adult volunteers, suggesting that dosage adjustment in the elderly might be considered when liver and renal function are significantly impaired.[21] At steady state, the C_{max} for manidipine and the M1 metabolite of delapril were increased by 35% and 24% in elderly subjects, while the respective AUC values were increased by 70% and 86% in elderly versus young adults.[21]

3. Therapeutic Efficacy

The antihypertensive efficacy of delapril/manidipine combination therapy in patients with mild to moderate essential hypertension has been assessed in at least eight clinical trials including >1700 patients.

Five studies have been fully published[11,22-25] and two others have been published as abstracts,[12,26] one of which[26] is supplemented by data from an oral presentation[27] and data on file with the manufacturer.[28] The published studies comprise a dose-finding study,[26] two nonblind studies of delapril/manidipine 30mg/10mg once daily in patients not responding to or intolerant of delapril or manidipine monotherapy,[22,24] three studies comparing delapril/manidipine 30mg/10mg once daily with other antihypertensive drug combinations[11,12,25] (although one study was not primarily designed as an efficacy evaluation[11]) and a long-term (50-week) noncomparative study of delapril/manidipine 30mg/10mg once daily.[23]

Results from an additional randomised, double-blind study comparing delapril/manidipine 30mg/10mg once daily with delapril or manidipine monotherapy are unpublished and derive from data on file with the manufacturer.[29]

Primary endpoints were specified in five studies and consisted of the reduction in sitting DBP,[22,25,29] reduction in sitting SBP/DBP[24] or the reductions in sitting SBP/DBP and pulse pressure.[23]

Dose Response

The optimum antihypertensive dosage of the delapril/manidipine combination was determined in a randomised, double-blind, placebo-controlled, multicentre study in 400 randomised patients of mean age 51.8 years with mild to moderate essential hypertension (mean sitting SBP/DBP of 159/101mm Hg).[26-28] The study used a 3 × 3 factorial design combining manidipine 5 or 10mg, delapril 15 or 30mg or placebo administered once daily for 6 weeks, following a 2-week placebo run-in period.

- Delapril/manidipine 30mg/10mg once daily was the most effective combination tested, producing a mean reduction from baseline in sitting, trough, cuff SBP/DBP of 15/13mm Hg.[27,28]
- The placebo-corrected mean reduction from baseline in sitting SBP/DBP with delapril/manidipine 30mg/10mg once daily was 11/9mm Hg and resulted in response or normalisation of BP in 72.7% of patients.[26,28]
- Combination treatment reduced mean sitting SBP and DBP to a significantly ($p < 0.05$–0.001) greater extent than equivalent doses of either manidipine or delapril alone, except for sitting SBP with manidipine 10 mg/day.[26,28]

Efficacy in Nonresponders to Monotherapy

The antihypertensive efficacy of delapril/manidipine 30mg/10mg once daily in nonresponders to monotherapy with either agent alone has been assessed in two studies.[22,24] In an open-label, multicentre, phase III study, patients were preselected for inadequate BP control (≈94% of patients), poor tolerability (≈5% of patients) or both (≈1% of patients) after previous monotherapy with delapril 30mg twice daily (n = 155) or manidipine 20mg once daily (n = 152).[22] In a substudy of an open-label, multicentre, phase III trial, patients were initially treated with delapril 30mg twice daily (n = 28) or manidipine 20mg once daily (n = 27) for 4 weeks, with nonresponders subsequently being treated for 8 weeks with combination delapril/manidipine 30mg/10mg once daily (n = 30).[24]

● In the larger study,[22] the mean reductions from baseline in sitting SBP/DBP after 12 weeks of combination therapy were 16/10mm Hg for nonresponders to manidipine and 16/11mm Hg for nonresponders to delapril (both $p < 0.01$ vs baseline). The proportion of patients responding (DBP reduction ≥10mm Hg) and/or with DBP normalisation (DBP ≤90mm Hg) ranged from 78% to 82% (figure 1).[22]

● In the substudy, combination therapy for an additional 8 weeks in nonresponders reduced mean sitting cuff SBP/DBP from baseline by 18/14mm Hg which was significantly ($p < 0.01$) greater than the reductions from baseline seen at 4 weeks with delapril (≈8/5mm Hg) and manidipine (≈10/4mm Hg).[24] Similar effects were observed with standing cuff BP and to a slightly lesser extent with 24-hour ambulatory BP.

Comparison with Monotherapy

● In a randomised, double-blind, multicentre study, the antihypertensive efficacy of the fixed combination delapril/manidipine 30mg/10mg once daily (n = 131) was compared with that of monotherapy with manidipine 10mg once daily (n = 134) or delapril 15mg twice daily (n = 136) for 12 weeks in patients with mild to moderate essential hypertension.[29]

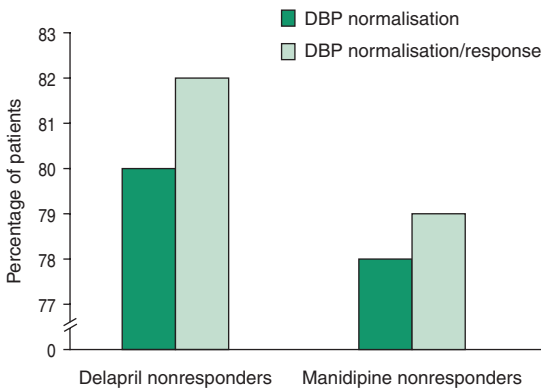

Fig. 1. Antihypertensive efficacy of delapril/manidipine combination therapy in nonresponders to previous monotherapy with delapril or manidipine: percentage of patients with mild to moderate essential hypertension achieving diastolic blood pressure (DBP) normalisation (DBP ≤90mm Hg), or normalisation or response (DBP reduction ≥10mm Hg) after treatment with delapril/manidipine 30mg/10mg once daily for 12 weeks.[22] Patients had previously failed to respond (≈94% of patients), had experienced poor tolerability (≈5%) or both (≈1%) after monotherapy with delapril 30mg twice daily (n = 155) or manidipine 20mg once daily (n = 152).[22]

● At week 12, the mean reduction from baseline in sitting, trough, cuff DBP was significantly greater with combination therapy (14mm Hg) than with delapril (10mm Hg; $p < 0.001$) or manidipine (11mm Hg; $p < 0.05$) monotherapy.[29]

● Similarly, the mean reduction from baseline in sitting SBP was significantly greater with combination therapy (19mm Hg) than with delapril (14mm Hg; $p < 0.01$) or manidipine (15mm Hg; $p < 0.05$) alone.[29]

● The proportion of diastolic responders (DBP ≤90mm Hg) at week 12 was 76% with delapril/manidipine, 57% with delapril alone and 64% with manidipine alone.[29] The respective proportions of systolic responders (SBP ≤140mm Hg) were 71%, 54% and 49%.

Comparisons with Other Combination Therapies

● In a randomised, multicentre study, patients with mild to moderate essential hypertension were treated once daily with delapril 30mg (n = 106) or enalapril 20mg (n = 54) for 8 weeks, and nonresponders (sitting DBP ≥85mm Hg) had manidipine 10mg (n = 72) or HCTZ 12.5mg (n = 28), respectively, added to their regimens for a further 8 weeks.[25] After 16 weeks, reductions in mean sitting and standing DBP and SBP were significantly ($p < 0.01$) greater than at 8 weeks in the combination therapy groups, with no differences between delapril/manidipine and enalapril/HCTZ recipients; 69% and 61%, respectively, were responders (DBP reduction ≥10mm Hg or DBP <85mm Hg).[25]

● In a randomised, multicentre study, patients with essential hypertension and type 2 diabetes (n = 425) received once-daily monotherapy with delapril 30mg, ramipril 2.5mg or valsartan 80mg for 6 weeks.[12] Nonresponders to delapril (n = 64) had manidipine 10mg added to their regimen, while nonresponders to ramipril (n = 73) and valsartan (n

= 52) had HCTZ 12.5mg added to their therapy for an additional 44 weeks. After 50 weeks, the proportions of patients controlled (DBP <85mm Hg) with delapril/manidipine, ramipril/HCTZ and valsartan/HCTZ were 59%, 47% and 60%, respectively. There were no significant between-group differences in the percentage of patients responding (DBP reduction ≥10mm Hg) or whose BP was controlled or normalised (DBP <90mm Hg).[12]

- In a double-blind, double-dummy, parallel-group study, patients with mild to moderate essential hypertension and type 2 diabetes were randomised to receive treatment with delapril 30mg once daily (n = 39) or irbesartan 150mg once daily (n = 37) for 8 weeks, after which manidipine 10mg was added to delapril and HCTZ 12.5mg was added to irbesartan for a further 8 weeks.[11] There were no significant differences in antihypertensive efficacy between the combination therapies. Mean SBP/DBP was reduced from 161/101mm Hg at baseline to 147/90mm Hg and 145/90mm Hg with delapril and irbesartan, respectively, at 8 weeks and to 134/80mm Hg with both delapril/manidipine and irbesartan/HCTZ after 16 weeks.[11]

Long-Term Efficacy

The long-term efficacy of delapril/manidipine 30mg/10mg once daily was assessed in a noncomparative, multicentre study in which 309 adult patients, aged 20–75 years, with mild to moderate essential hypertension received active treatment for 50 weeks, following a 2-week, single-blind, placebo run-in period.[23] Non-elderly patients with DBP >95mm Hg at 4 weeks and elderly patients with DBP >95mm Hg at 8 weeks received add-on therapy with HCTZ 12.5mg once daily (n = 93).[23]

- The antihypertensive efficacy of delapril/manidipine 30mg/10mg once daily was maintained in the long-term.[23] Clinically significant mean reductions from baseline in SBP/DBP (17/9mm Hg) were apparent after 4 weeks of treatment, reaching 22/14mm Hg at 50 weeks. Mean pulse pressure was reduced from 61mm Hg at baseline to 54mm Hg after 1 month of treatment, where it remained after 50 weeks.[23]
- At 50 weeks, the proportion of patients responding to treatment (DBP reduction ≥10mm Hg) or experiencing normalisation of DBP (DBP ≤90mm Hg) was 86.4%, while normalisation of DBP was achieved in 80.6% of patients. Systo-diastolic control (SBP/DBP ≤140/90mm Hg) was attained in 55.3% of patients and optimal DBP control (DBP ≤85mm Hg) in 53.7% (figure 2).[23]

4. Tolerability

Tolerability data for delapril/manidipine were obtained from clinical trials discussed in section 3.[12,22,23,25-29] Delapril and manidipine monotherapy data sources were the manufacturer's prescribing information[17,30] and an earlier review.[8]

- The most common adverse events with manidipine monotherapy are ankle oedema, headache, palpitations, flushing and dizziness,[8,17] while those for delapril are dizziness and vertigo, headache, nausea and vomiting, cough and fatigue.[30]
- Combination therapy with delapril/manidipine was generally well tolerated. In the dose-finding study (section 3), only 1% of patients withdrew as a

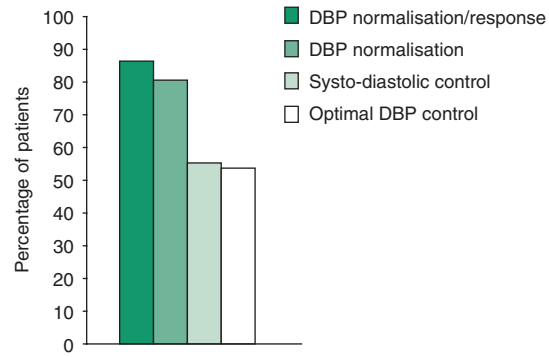

Fig. 2. Long-term antihypertensive efficacy of delapril/manidipine. Effect of treatment with delapril/manidipine 30mg/10mg once daily for 50 weeks in adult patients, aged 20–75 years, with mild to moderate essential hypertension (n = 309) on the proportion of patients responding to treatment (reduction in diastolic blood pressure [DBP] ≥10mm Hg) and/or achieving DBP normalisation (DBP ≤90mm Hg), systo-diastolic control (DBP ≤90mm Hg and systolic BP ≤140mm Hg) or optimal DBP control (DBP ≤85mm Hg).[23]

result of adverse events, with no differences between any of the treatment groups.[26] Adverse events were typical of those associated with the component monotherapies, with no unexpected adverse effects.[28]

- In the phase III study (section 3), the tolerability of delapril/manidipine was similar to those of its component monotherapies. Thirty percent of patients reported adverse events during 12 weeks of treatment with delapril/manidipine 30mg/10mg once daily; an incidence similar to those for monotherapy with delapril (33%) or manidipine (29%).[29] The respective incidences of patients experiencing adverse events considered drug-related were 7%, 6% and 10%; most commonly cough with delapril/manidipine and delapril, and flushing with manidipine. Most events were well recognised adverse effects of the individual agents and were of mild to moderate severity.[29]
- Of 15 patients who had experienced poor tolerability to previous delapril or manidipine monotherapy (section 3), all but three were free of adverse events during 12 weeks of delapril/manidipine combination therapy.[22]
- The incidence of adverse events with delapril/manidipine was similar to that with enalapril/HCTZ,[25] ramipril/HCTZ[12] or valsartan/HCTZ,[12] although ramipril/HCTZ and valsartan/HCTZ, but not delapril/manidipine, increased serum creatinine from baseline (see section 1).[12]
- During long-term therapy for 50 weeks with delapril/manidipine (section 3), 43.4% of patients reported adverse events, although a possible relationship to therapy was only apparent in 14.2% of patients.[23] Only one patient experienced a drug-related serious adverse event (anxiety disorder). The most frequent adverse events were headache (7.1%), cough (5.2%), bronchitis (3.9%), ankle/leg oedema (3.2%) and anxiety (2.6%). Fifteen patients withdrew from therapy as a result of adverse events.[23]
- Treatment of patients (n = 30) with manidipine 10mg once daily, but not delapril 30mg once daily, for 4 weeks significantly ($p < 0.001$ vs placebo) elevated pretibial subcutaneous tissue pressure (+9.9%) and ankle-foot volume (+8.7%) [published as an abstract].[31] However, after treatment with combination delapril/manidipine 30mg/10mg once daily, the increases in these measures of ankle oedema (+5.1% and +4.2%, respectively) were significantly ($p < 0.01$ and $p < 0.05$, respectively) less than those with manidipine alone.[31]

5. Dosage and Administration

The recommended usual dosage of the delapril/manidipine 30mg/10mg fixed combination tablet in adults is one tablet administered orally once daily after breakfast.[32] The combination tablet is contraindicated in children and adolescents.

Dose titration with the individual components (delapril and manidipine) is generally recommended.[32] Dose titration should be performed with caution in elderly patients and a half-tablet of the fixed combination may be considered initially in these patients.

Dosage adjustment is necessary in patients with serum creatinine >3 mg/dL and should be considered in patients with more severe hepatic impairment.[32]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Delapril/Manidipine: Current Status

The delapril/manidipine 30mg/10mg fixed combination tablet has been approved in Austria, Brazil, Germany, Greece, Italy and Spain for the treatment of essential hypertension in adults whose BP is not adequately controlled on delapril or manidipine alone.

The fixed combination has been shown in clinical trials to be an effective and well tolerated antihypertensive therapy. Clinical trials have demonstrated its efficacy in patients with a poor response to delapril or manidipine monotherapy and in the long-term treatment of essential hypertension. Delapril/manidipine was as effective as enalapril/HCTZ in hypertensive patients unresponsive to monotherapy with the respective ACE inhibitor.

Similarly, delapril/manidipine was as effective as ramipril/HCTZ, valsartan/HCTZ or irbesartan/HCTZ in patients with hypertension and type 2 diabetes.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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