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Barnidipine

Harinder S. Malhotra and *Greg L. Plosker*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Barnidipine is an antihypertensive drug belonging to the dihydropyridine (DHP) group of calcium antagonists. It is available in a modified-release formulation which has a gradual onset of action and is effective in a single daily oral dose of 10 to 20mg.

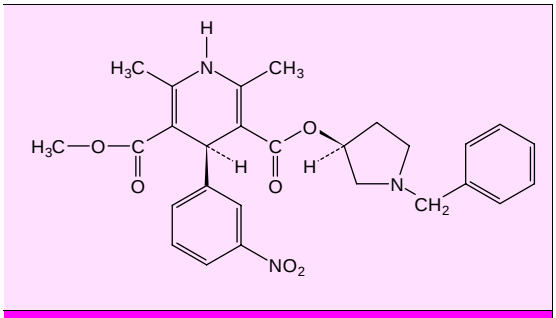
▲ Barnidipine has selective action against cardiovascular calcium antagonist receptors and its antihypertensive action is related to the reduction of peripheral vascular resistance secondary to its vasodilatory action.

▲ The clinical antihypertensive efficacy of barnidipine is similar to that of other DHP calcium antagonists such as nitrendipine and amlodipine, and antihypertensives belonging to other drug classes such as atenolol and enalapril.

▲ Barnidipine has been found to be as efficacious and well tolerated as hydrochlorothiazide in the management of hypertension in elderly patients.

▲ Barnidipine is generally well tolerated. As with other DHP calcium antagonists, vasodilator adverse events such as headache, flushing and peripheral oedema account for most of the adverse events reported with its use and are usually transient. Oedema is less frequent than with amlodipine and nitrendipine. Its use is not associated with reflex tachycardia.

Features and properties of barnidipine (mepirodipine, YM097305, LY198561)	
Indications	
Treatment of mild to moderate hypertension	
Therapeutic class	
Antihypertensive	Highly selective dihydropyridine calcium antagonist with gradual onset of action
Dosage and administration (modified-release formulation)	
Recommended dosage	10-20 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Special patient groups	No dosage modification required in elderly and patients with diabetes mellitus
Pharmacokinetic profile (after single 10mg dose, modified-release formulation)	
Peak plasma concentration	0.48 μg/L
Area under the plasma concentration-time curve	2.85 μg/L • h
Tolerabilty	
General	Well tolerated; does not produce reflex tachycardia
Most frequent adverse events	Headache, flushing, peripheral oedema



Barnidipine

Calcium antagonists (calcium channel blockers) have been extensively used for the treatment of hypertension. Their antihypertensive efficacy is similar to that of β-blockers, angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics.[1] Dihydropyridine (DHP) calcium antagonists have been shown to reduce the incidence of stroke among elderly patients with systolic hypertension and are particularly recommended in this group of patients.[1,2] They are also useful as alternatives to ACE inhibitors in patients with hypertension and systolic heart failure.[3] DHP calcium antagonists make effective drug combinations with β-blockers and with ACE inhibitors for the treatment of patients with hypertension.[2] Association of an increase in cardiovascular events with the use of short-acting nifedipine has not been observed with long-acting DHP calcium antagonists.[1]

Barnidipine is a DHP calcium antagonist that, like other members of this drug class, is selective for L-type calcium channels. It is composed of a single optical isomer (*S*,*S* configuration) and is available in a modified-release formulation for once daily oral administration in the treatment of patients with mild to moderate hypertension.

1. Pharmacodynamic Profile

Barnidipine produces its antihypertensive effect by selective blockade of calcium ion influx via the L-subtype 'voltage-operated' channels in the excitable membranes of vascular smooth muscle cells, as a result of interaction with specific L-type calcium channel receptors.

Receptor Binding

- Orally administered barnidipine produced selective and sustained occupancy of cardiovascular calcium antagonist receptors in spontaneously hypertensive rats (SHR).[4] This effect was maximal (69%) at 0.5 hours and was still evident at 6 hours (41%). The maximum occupancy of receptors in the cerebral cortex was only 34%. The fall in blood pressure in these rats correlated significantly with the occupancy of cardiac calcium antagonist receptors by barnidipine ($r = 0.98$, $p < 0.05$).

- The binding of calcium antagonist receptors by barnidipine correlates well with its plasma concentration.[5] The plasma concentration required to occupy calcium antagonist receptors in brain tissue was 20 times that required for cardiac tissue, suggesting selectivity towards cardiovascular receptor binding by the drug.

Haemodynamic Studies

- The barnidipine molecule contains 2 chiral centres and can therefore have 4 enantiomers.[6] The 3′*S*,4*S* enantiomer (barnidipine) produced much more potent relaxation of guinea-pig aorta *in vitro* (33- to 118-fold) and dilatation of the coronary artery in anaesthetised dogs *in vivo* (2.8- to 16-fold) than the other enantiomers.

- The effect of barnidipine on vascular smooth muscle in guinea-pig isolated aorta was 7, 8 and 13 times greater than that with nicardipine, nitrendipine and nifedipine, respectively (fig. 1.).[6] The vasodilatory effect on the coronary artery in anaesthetised dogs was slower in onset and had a longer duration of action than with these calcium antagonists.[6] In a study on isolated mesenteric artery preparations in Wistar rats, barnidipine showed a more potent vasodilator effect and a slower onset of action than the other calcium blockers.[7] The gradual onset of action of the drug is because of its lipophilic nature and the modified-release formulation.[8]

- Barnidipine significantly reduced peripheral vascular resistance by 21.1% ($p < 0.01$) while achieving a mean reduction of 13.8% in blood pres-

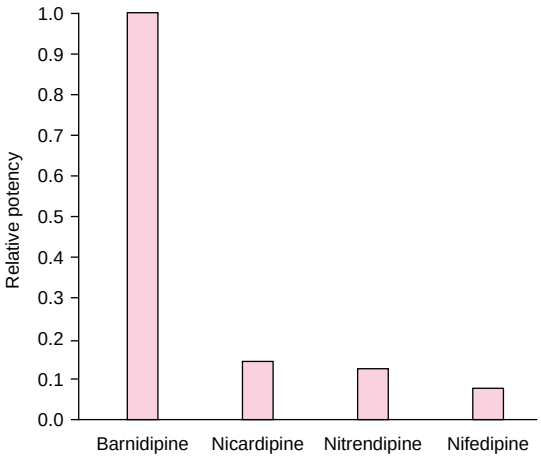


Fig. 1. Comparison of relative potency of inhibitory effects of various calcium antagonists on potassium chloride-induced contractions in guinea-pig isolated aorta.[6]

sure in 10 patients with hypertension who received 15mg of the drug daily for 4 weeks.[9] The regional renal (–19.2%, $p < 0.01$) and hepatic (–17.6%, $p < 0.01$) vascular resistance fell considerably and reductions in mean arterial pressure correlated with those in renal vascular resistance ($r = 0.699$, $p < 0.05$).

- Barnidipine did not produce any reflex tachycardia[9-11] or any fall in left ventricular ejection fraction[10] in patients with hypertension receiving the drug over variable periods of time.

- In *in vitro* studies with canine isolated perfused heart preparations, barnidipine showed a 7-fold higher selectivity against cardiac contractility but was less selective against sino-atrial automaticity and atrio-ventricular nodal conduction than nifedipine.[12]

Renal Effects

- Barnidipine 10^{-7} mol/L significantly dilated both afferent and efferent arterioles and increased glomerular blood flow in hypertensive rats by use of the *in vivo* split hydronephrotic kidney model.[13]

- Barnidipine reduced proteinuria and the expression of messenger RNA of platelet derived growth factor B-chain, a factor involved in hypertensive renal injury, in the glomeruli of SHR.[14] This is probably related to the antihypertensive effect of the drug.

Effect on Neurohumoral Activation

- Barnidipine 10 to 20 mg/day, given over 4 to 12 weeks to patients with mild to moderate hypertension, produced a significant fall in plasma noradrenaline levels. There was no significant change in plasma noradrenaline levels in patients receiving nitrendipine 10 to 20 mg/day.

Barnidipine and nitrendipine had no significant effect on plasma levels of adrenaline, dopamine, aldosterone or vasopressin in patients with hypertension.[10]

Metabolic Effects

- Barnidipine, when studied in non-obese hypertensive patients over 12 weeks, improved insulin sensitivity as measured using the euglycaemic hyperinsulinaemic clamp technique.[15]

- No significant changes in serum levels of total cholesterol, triglycerides or high density lipoprotein cholesterol were observed in 18 patients with hypertension receiving barnidipine 15mg once daily for 12 weeks.[15]

2. Pharmacokinetic Profile

Absorption and Distribution

- Barnidipine is readily absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism.[16] The absolute bioavailability of the modified-release formulation of barnidipine studied following a single 6-hour, 0.75mg infusion and a single 20mg oral dose in healthy volunteers was 1.1%.[8]

- *In vitro* binding of barnidipine with plasma proteins was between 92.4 and 98.9%, and was mainly with albumin.[16] Protein binding assays showed

no interaction with drugs such as amitryptyline, diazepam, diclofenac, phenytoin and warfarin.[8]

• Bioavailability of the modified-release formulation of barnidipine was not significantly affected by food intake (including grapefruit juice) in healthy volunteers, nor were the pharmacokinetics of this formulation affected by age, gender or renal function.[16]

• Area under the plasma concentration-time curve (AUC) achieved with the modified-release formulation (2.85 μg/L · h) was 97% of that with the conventional formulation in a crossover study of 6 healthy volunteers.[17] Peak plasma concentration of barnidipine after a single 10mg dose of the modified-release formulation was 0.48 μg/L.[17]

• After administration of single oral doses of radiolabelled barnidipine in rats, levels of radioactivity were found to be higher in the kidney, liver and gastrointestinal tract than in plasma, whereas the brain showed the lowest level of radioactivity.[16]

Metabolism and Elimination

• Barnidipine is extensively metabolised to a number of metabolites, all of which are inactive.[16] The primary metabolic pathways in humans are oxidation of the dihydropyridine ring and ester hydrolysis of the side chain.[16] Urinary excretion of unchanged drug was negligible (≤0.003% of an administered dose) after single dose administration of barnidipine 5 to 20mg in healthy volunteers.[18] On the basis of animal data, the drug does not appear to be excreted in the bile unchanged.[16] The drug is detected in breast milk.[8]

• The median terminal elimination half-life of barnidipine was 20 hours after repeated administration, according to a 2-compartment analytical model.[8]

• *In vitro* studies involving incubation of radiolabelled and unlabelled barnidipine with human liver microsomes under various conditions revealed the involvement of cytochrome P450 3A isoenzymes in the primary as well as secondary metabolic pathways.[19]

• The rate of formation of the primary metabolites of barnidipine *in vitro* in a human microsomal system was not affected by high concentrations (200 μmol/L) of warfarin, theophylline, phenytoin, diclofenac or amitriptyline.[19] However, it was inhibited by glibenclamide (glyburide), simvastatin and cyclosporin in concentrations that were 200, 6000 and 50 times higher than their respective therapeutic plasma levels.

• Plasma barnidipine levels are 3 to 4 times higher in patients with mild to moderate hepatic dysfunction than in healthy volunteers. Barnidipine is therefore contraindicated in patients with hepatic insufficiency.[8] However, no dosage modification is required in elderly patients and those with diabetes mellitus.[8]

3. Therapeutic Trials

The antihypertensive efficacy of barnidipine has been evaluated in a number of dose-ranging, placebo-controlled and comparative trials. Patients with mild to moderate hypertension, generally defined as diastolic blood pressure (DBP) of 95 to 114mm Hg at the end of a 2- to 4-week placebo run-in period, were included in most studies. All studies involved once daily administration of the drug with changes from baseline in trough (end of dosage interval) sitting DBP as the primary endpoint in most. Several studies reported response rate, which was usually defined as trough sitting DBP of ≤90mm Hg or ≥10mm Hg reduction from baseline.

Dose-Ranging and Noncomparative Studies

• A trend towards a dose-response relationship was demonstrated with barnidipine in a dose-ranging, multicentre, placebo-controlled, double-blind study in 190 patients with mild to moderate hypertension.[20] Barnidipine 10 and 20 mg/day achieved reductions in DBP of up to 8.5mm Hg and antihypertensive response rates of 44 and 49%, respectively, after 6 weeks of treatment.

• 91% of 106 patients who had initially responded to the drug after 6 to 12 weeks of therapy main-

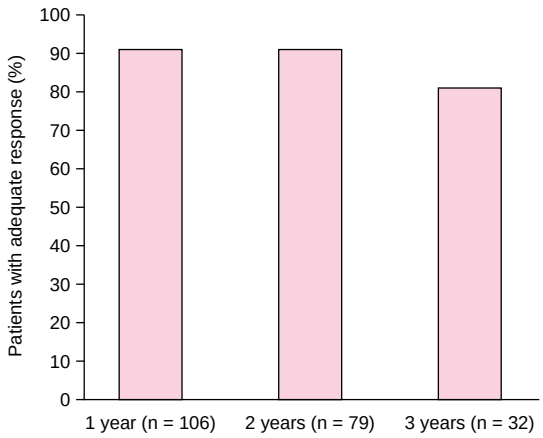


Fig. 2. Patients maintaining an antihypertensive response with continued use of barnidipine 10 to 40 mg/day at end of 1, 2 and 3-year follow-up periods. All patients had initially responded to 6 to 12 weeks of barnidipine therapy.[21]

tained the response at the end of a 1-year follow-up period with dosages ranging from 10 to 40 mg/day.[21] The antihypertensive response was maintained in 91% of 79 patients who completed a 2-year follow-up, with over 60% of patients remaining on barnidipine monotherapy (10 or 20 mg/day) at the end this period. 81% of the 32 patients who completed a 3-year follow-up continued to have well controlled blood pressure (fig. 2).

- In a study measuring 24-hour ambulatory blood pressure in 34 patients with mild to moderate hypertension, nocturnal systolic blood pressure (SBP) and daytime DBP did not fall in patients with false hypertension.[22]

- In a placebo-controlled, double-blind, crossover study measuring 24-hour ambulatory blood pressure in 20 patients, barnidipine 20 mg/day for 6 weeks, significantly reduced mean 24-hour, daytime and night-time blood pressure compared with placebo.[23] The mean trough to peak ratios of antihypertensive efficacy were 0.82 for SBP and 0.71 for DBP, reflecting well balanced blood pressure control over 24 hours.

- Barnidipine produced adequate reduction in blood pressure (defined as a reduction of >20mm Hg in SBP or >10mm Hg in DBP) in 25 of 31 (80.6%) patients with renal parenchymal hypertension (mean baseline SBP and DBP levels of 170 and 110 mm Hg, respectively) at the end of an 8-week treatment period.[24]

Comparison with Other Calcium Antagonists

- Barnidipine has been compared with nitrendipine and amlodipine in 2 European multicentre, randomised, double-blind trials of 12 weeks' duration in patients with mild to moderate hypertension.[25] In the nitrendipine comparative study in 142 patients, the mean fall in DBP with barnidipine 10 to 20 mg/day was similar to that with nitrendipine 10 to 20 mg/day (11.6 *vs* 12.5mm Hg) [fig. 3]. The percentage of patients who responded with a reduction in DBP to 90mm Hg or less was also similar in the 2 groups (61 *vs* 62%).

- In the amlodipine comparative study (n = 116), the mean reduction in DBP with barnidipine 10 to 20 mg/day (16.6mm Hg) was similar to that with amlodipine 5 to 10 mg/day (16.9mm Hg) [fig. 3; p-values not provided].[25] The response rate was similar in the 2 groups (data not provided).

Comparison and Use with Other Antihypertensives

- In a multicentre, double-blind, randomised study involving 247 patients with mild to moderate hypertension, the response rate with barnidipine 20 mg/day was similar to that with atenolol 50mg/day (53 *vs* 58%) after 6 weeks.[26] Barnidipine, when added to atenolol in patients not responding to the latter, produced a further mean reduction of 11.3 and 5.5mm Hg in SBP and DBP, respectively, over another 6-week period.

- The response rate with barnidipine 20 mg/day was similar to that with enalapril 20 mg/day (60 *vs* 73%) in a randomised, double-blind trial in 155

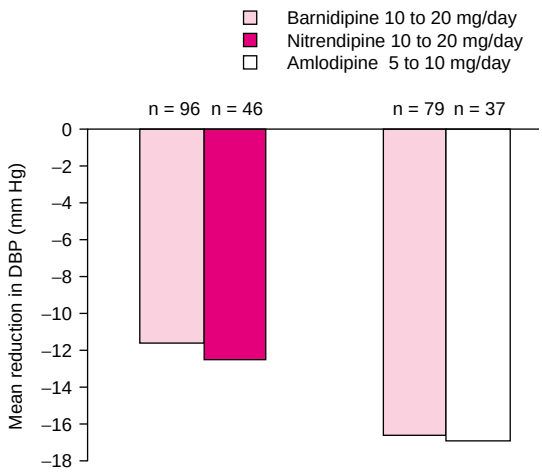


Fig. 3. Mean reduction in diastolic blood pressure (DBP) in patients with mild to moderate hypertension in 2 double-blind, randomised, multicentre studies of 12 weeks' duration comparing barnidipine with nitrendipine and amlodipine.[25]

patients with mild to moderate hypertension over a 12-week period.[26] Addition of enalapril produced a response in 57% of patients not responding to barnidipine monotherapy. In patients who did not respond to enalapril, switching to barnidipine monotherapy resulted in a response in 68%.

Use in Elderly

• A response rate of 84% was achieved with barnidipine 10 to 20 mg/day or hydrochlorothiazide 12.5 to 25 mg/day at the end of 18 weeks in a double-blind study in 315 elderly patients (aged ≥75 years) with mild to moderate hypertension.[27] Reductions from baseline in sitting DBP were 14.5 and 14.9mm Hg, respectively.

• Barnidipine 10 to 20 mg/day, given for 8 weeks, was effective in lowering DBP to below 90mm Hg in 74% of 236 elderly patients (aged ≥75 years) with hypertension in a nonblind multicentre study.[28] Another 10.1% of patients responded with the addition of an ACE inhibitor or a diuretic. The overall mean sitting DBP fell by 18.4mm Hg, from 102.1mm Hg to 83.7mm Hg.

4. Tolerability

• Barnidipine has been well tolerated in clinical trials. Combined data from 5 pivotal European studies in a total of 634 patients with hypertension showed the following adverse events with barnidipine 10 mg/day: headache (4.3%), flushing (4.3%), peripheral oedema (2.7%), dizziness (2.3%) and palpitations (1.9%).[29] The incidence was higher with a starting dose of 20 mg/day but lower if the dose was titrated from 10 to 20 mg/day. Most adverse effects were mild to moderate in intensity and between 2 and 9% of patients receiving a dose of 10 mg/day withdrew from the studies. Most adverse events occur early in the course of barnidipine therapy and are often transient.[8]

• In a multicentre study in which 106 patients who initially responded to 6 to 12 weeks of barnidipine were followed up for 1 year, 23 (22%) reported at least 1 adverse event considered to be related to the drug.[21] Of the 79 patients who completed a 2-year follow-up period, 11 (14%) reported drug-related adverse events during the second year.

• Adverse events reported with the use of barnidipine were similar to those with nitrendipine and amlodipine in multicentre, double-blind studies.[25] Oedema was less frequent with the use of barnidipine than with nitrendipine (2.1 *vs* 10.9%, respectively) and amlodipine (3.8 *vs* 5.4%, respectively). Adverse events such as palpitations, rash and diarrhoea that occurred in patients receiving amlodipine were not observed with the use of barnidipine.[25]

• In a multicentre, double-blind study, the incidence of at least 1 reported adverse event was lower when barnidipine was used in combination with atenolol than when used as monotherapy (24 *vs* 39%, respectively).[26] Similarly, fewer patients (7%) receiving a combination of barnidipine and enalapril experienced adverse events than those receiving barnidipine monotherapy (24%).[26]

• In a 2-year follow-up study in 236 elderly patients with hypertension receiving up to 20 mg/day of barnidipine (an ACE inhibitor or diuretic was added in 58 patients), 89 patients (37.7%) experienced an adverse event related to therapy.[28] The pattern of these adverse events was similar to that observed in other studies in younger patients. Serious events occurred in 50 patients (21.2%) but the majority (86%) of them were considered to be unrelated to the study medication. The drug was withdrawn because of adverse events in 52 patients (22%).

• In another study in 315 elderly patients with hypertension comparing barnidipine with hydrochlorothiazide, the incidence of adverse events was similar between the 2 drugs (69.2 *vs* 60.3%).[27] Serious adverse events occurred in 24 patients (7.6%) but in only 2 (tachycardia crisis and an episode of chest pain) were they attributable to barnidipine.

5. Barnidipine: Current Status

Barnidipine is a DHP calcium antagonist that is available in a modified-release formulation for once daily administration in the treatment of patients with mild to moderate hypertension. It has shown clinical antihypertensive efficacy which is similar to that of other DHP calcium antagonists, as well as atenolol and enalapril. It has also been shown to be as efficacious as hydrochlorothiazide in the management of hypertension in the elderly. Barnidipine is well tolerated and adverse effects with its use are similar to those associated with other DHP calcium antagonists. Oedema is less frequent with barnidipine than with nitrendipine or amlodipine. It does not produce reflex tachycardia.

References

1. Ramsay LE, Williams B, Johnston GD, et al. British Hypertension Society guidelines for hypertension management 1999: summary. BMJ 1999 Sep 4; 319: 630-5
2. Alderman M, Arakawa K, Beilin L, et al. 1999 World Health Organization – International Society of Hypertension Guidelines for the Management of Hypertension. Blood Press 1999; 8 Suppl. 1: 9-43
3. Singh V, Christiana J, Frishman WH. How to use calcium antagonists in hypertension: putting the JNC-VI guidelines into practice. Drugs 1999 Oct; 58: 579-87
4. Yamada S, Matsuoka Y, Kato Y, et al. A sustained occupancy *in vivo* of cardiovascular calcium antagonist receptors by mepirodipine and its relation to pharmacodynamic effect in spontaneously hypertensive rats. J Pharmacol Exp Ther 1992 Aug; 262: 589-94
5. Yamada S, Matsuoka Y, Kimura R. Correlation between the plasma concentration of mepirodipine and its occupancy of Ca2+ antagonist receptors in rats. Pharm Res 1993 Sep; 10: 1346-9
6. Inagaki O, Asano M, Takenaka T. *In vitro* and *in vivo* vasodilatory activity of barnidipine and its enantiomers. Biol Pharm Bull 1999 Feb; 22: 151-6
7. van-der-Lee R, Kam KL, Pfaffendorf M, et al. Differential time course of the vasodilator action of various calcium antagonists. Fundam Clin Pharmacol 1998; 12: 607-12
8. VasextenTM monograph. Yamanouchi Europe B.V
9. Noda H, Fujita T, Ogata E. The role of renal hemodynamics in the antihypertensive action of mepirodipine, a new calcium antagonist. Jpn Circ J 1992 Jan; 56: 21-6
10. Argenziano L, Izzo R, Iovino G, et al. Distinct vasodilation, without reflex neurohormonal activation, induced by barnidipine in hypertensive patients. Blood Press Suppl 1998; 1: 9-14
11. Ohya Y, Abe I, Ohta Y, et al. Natriuretic effect of barnidipine, a long-acting dihydropyridine calcium channel blocker, in patients with essential hypertension. Int J Clin Pharmacol Ther 2000 Jun; 38: 304-8
12. Motomura S, Hashimoto K. Reconsideration of vascular selectivity of dihydropyridine calcium antagonists: comparison of cardiovascular profile of mepirodipine, a novel dihydropyridine consisting of a single stereoisomer with (+)-(S)-(S) conformation, with those of nifedipine and nicardipine. Jpn J Pharmacol 1990 Feb; 52: 319-30
13. Kimura K, Suzuki N, Mise N, et al. Effects of barnidipine hydrochloride, a calcium channel blocker, on renal microcirculation in rats: A pilot study. Curr Ther Res Clin Exp 1998; 59 (12): 826-34
14. Hashimoto M, Yamauchi T, Ogura T, et al. Treatment with a Ca(2+) channel blocker, barnidipine, reduces platelet-derived growth factor B-chain mRNA in glomeruli of spontaneously hypertensive rats. Am J Nephrol 1999; 19: 615-21
15. Kosegawa I, Inaba M, Morita T, et al. Effect of the vasodilatory beta-blocker, nipradilol, and Ca-antagonist, barnidipine, on insulin sensitivity in patients with essential hypertension. Clin Exp Hypertens 1998 Oct; 20: 751-61
16. Sakai T, Teramura T, Okamiya H, et al. A review on barnidipine: a novel calcium antagonist. Cardiovasc Drug Rev 1997; 15 (4): 273-90
17. Teramura T, Watanabe T, Higuchi S, et al. Metabolism and pharmacokinetics of barnidipine hydrochloride, a calcium channel blocker, in man following oral administration of its sustained release formulation. Xenobiotica 1997 Feb; 27: 203-16
18. Teramura T, Tokunaga T, Matsumoto H, et al. Metabolism of barnidipine hydrochloride, a potent calcium antagonist, in rat and dog. Xenobiotica 1996 Feb; 26: 177-87
19. Teramura T, Fukunaga Y, Van-Hoogdalem EJ, et al. Examination of metabolic pathways and identification of human liver cytochrome P450 isozymes responsible for the metabolism of barnidipine, a calcium channel blocker. Xenobiotica 1997 Sep; 27: 885-900
20. Hart W, Holwerda NJ. Barnidipine, a novel calcium antagonist for once-daily treatment of hypertension: a multicenter, double-blind, placebo-controlled, dose-ranging study. Dutch Barnidi-

pine Multicenter Study Group. Cardiovasc Drugs Ther 1997 Nov; 11: 637-43
21. Smilde JG. The long-term efficacy and safety profile of barnidipine. Int J Clin Pract 2000 Nov; 114 Suppl.: 20-6
22. Imai Y, Abe K, Nishiyama A, et al. Evaluation of the antihypertensive effect of barnidipine, a dihydropyridine calcium entry blocker, as determined by the ambulatory blood pressure level averaged for 24h, daytime, and nighttime. Barnidipine Study Group. Am J Hypertens 1997 Dec; 10 (12 Pt 1): 1415-9
23. Smilde JG, Holwerda NJ, Lustermans FAT. Impact of barnidipine on 24-hour ambulatory blood pressure in patients with mild to moderate esential hypertension. J Hypertens 2000 Jun; 18 Suppl. 2: 56
24. Huh WS, Kim YS, Han JS, et al. Antihypertensive efficacy and tolerability of barnidipine hydrochloride in patients with renal parenchymal hypertension. Curr Ther Res Clin Exp 2000 Jul; 61: 395-405
25. Spieker C. Efficacy and tolerability of once-daily barnidipine in the clinical management of patients with mild to moderate essential hypertension. Blood Press Suppl 1998; 1: 15-21
26. Ruilope LM, Coca A. The role of combination therapy in the treatment of hypertension. Blood Press Suppl 1998; 1: 22-6
27. Otterstad JE, Ruilope LM. Treatment of hypertension in the very old. Int J Clin Pract 2000 Nov; 114 Suppl.: 10-9
28. Naber FB, Hage R, Mortelmans J. Barnidipine monotherapy and combination therapy in older patients with essential hypertension: a long-term study. Int J Clin Pract 2000 Nov; 114 Suppl.: 27-35
29. van-der-Velden JW, Beudeker HJ, Nishi M. Diversity and intensity of adverse events in the treatment of hypertension with barnidipine. Blood Press Suppl 1998; 1: 27-9

Correspondence: *Harinder S. Malhotra,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz