RESEARCH

Tolerability of High Doses of Lercanidipine versus High Doses of Other Dihydropyridines in Daily Clinical Practice: The TOLERANCE Study

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The TOLERANCE study was aimed to compare the tolerability of high doses of lercanidipine (20 mg) with that of other frequently used dihydropyridines (amlodipine 10 mg/nifedipine GITS 60 mg) in the treatment of essential hypertension in daily clinical practice. It was an observational, transversal, multicentre study performed in a Primary Care Setting. A total of 650 evaluable patients with essential hypertension and age $\geq$ 18 years were included. They had been treated with high doses of lercanidipine ($n = 446$) or amlodipine/nifedipine GITS ($n = 204$) during at least 1 month and previously with low doses (10 mg, 5 mg, and 30 mg, respectively) of the same drugs. The main objective was to compare the rates of vasodilation-related adverse events between both groups. Rates of signs and symptoms related to vasodilation were significantly higher ($P < 0.001$) in the amlodipine/nifedipine GITS group (76.8%, CI 95% [70.7; 82.9]) than in lercanidipine group (60.8%, [56.1;65.5]). Blood pressure control (< 140/90 mmHg or <130/80 for diabetics) and type of concomitant antihypertensive medications were similar in both groups. Treatment compliance was good (around 93%) and fairly comparable in both groups. Most adverse events with lercanidipine were mild (74.5% vs. 64% in amlodipine/nifedipine GITS group, $P = 0.035$) whereas severe adverse event rates did not differ significantly between groups (2.8% vs. 3.6%). In conclusion, treatment with lercanidipine at high doses is associated with a lower rate of adverse events related to vasodilation compared to high doses of amlodipine or nifedipine GITS in clinical practice.

Introduction

Hypertension is a major public health problem due to its high prevalence and close relationship with cardiovascular events. But, current blood pressure (BP) control rates are still far from the target of 50% proposed for the year 2010 (USHHS 2006). It has been demonstrated in recent clinical trials that BP control can only be achieved with two or more antihypertensive drugs in most cases (Cushman et al. 2002; ESH 2003). The poor control of hypertension may be partially due to the low treatment compliance of the patients. Some factors that have been involved in this poor compliance are adverse events related to antihypertensive drugs, lifelong treatment, and polymedication (Osterberg and Blaschke 2005). Calcium channel blockers (CCB) are widely used drugs for the treatment of hypertension. Lercanidipine is a highly lipohilic third generation dihydropyridine (DHP) (Bang et al. 2003). Its antihypertensive effect results from peripheral vasodilation and decreased total peripheral resistance (Meredith 1999). This drug has a slow onset of action due to its high lipophilicity and its partitioning into the lipid bilayer of cell membranes, followed by diffusion to the receptor binding site, that helps to avoid reflex tachycardia associated with other DHP, such as nifedipine (Ambrosioni and Circo 1997; Meredith 1999). Its

efficacy has been evaluated in noncomparative (Barrios et al. 2002; Viviani 2002; Barrios et al. 2006a; Barrios et al. 2006b) and comparative studies (Agrawal et al. 2006; James et al. 2002; Millar-Craig et al. 2003;). In most trials the starting dose was 10 mg/day. Lercanidipine is generally well tolerated during monotherapy in patients with mild-to-moderate hypertension (Barrios et al. 2002; Borghi et al. 2003). Because in older population the occurrence of side effects is more likely, the use of well-tolerated drugs is particularly important in these patients. Lercanidipine has been shown to be safe even in the elderly (Barbagallo and Barbagallo Sangiorgi 2000; Leonetti et al. 2002).

DHP-related adverse events are generally associated with vasodilation and include headache, dizziness, flushing, or edema (Leonetti 1999). In previous studies lercanidipine has been compared to other DHP such as nitrendipine (Rengo and Romis 1997), nifedipine SR (Policicchio et al. 1997), and nifedipine gastrointestinal therapeutic system (GITS) (Cherubini et al. 2003; Romito et al. 2003) with a lower incidence of adverse events favoring lercanidipine. Nonetheless, this information is derived from clinical trials with commonly strict inclusion and exclusion criteria with less information available from "real world" clinical settings.

The main objective of the TOLERANCE (TOlerabilidad de LERcanidipino 20 mg frente a Amlodipino y Nifedipino en **C**ondicionEs normales de uso) study was to compare the tolerability, with special emphasis on vasodilation-related adverse reactions, of high doses of lercanidipine with other DHP (amlodipine and nifedipine GITS) also given at daily high doses. The study was performed in Primary Care setting in conditions of common clinical practice.

Methods

It was an observational, cross-sectional and multicenter study performed in Primary Care Centers from all around Spain. The study population were outpatients aged $\geq$ 18 years with essential hypertension who had been treated at least for 1 month with lercanidipine, amlodipine, or nifedipine GITS at low doses (10, 5, and 30 mg daily, respectively) and who were titrated to higher doses of the same drugs (20, 10, and 60 mg, respectively) in a 2:1:1 design because of a BP below target. They should have been treated with these high doses during at least 1 month before entering the study (Figure 1). Patients with heart failure were excluded. Subjects had to give their written informed consent to participate in the study. The study was evaluated and approved by the Ethics Committee of the Ramon y Cajal University hospital in Madrid.

The main objective of the study was to determine the rates of adverse events linked to vasodilation in patients treated with lercanidipine 20 mg. This prevalence was compared with that of a group of subjects treated with amlodipine or nifedipine GITS at high doses. Other objectives were: (1) Evaluate the frequency of the commonest adverse reactions associated to lercanidipine (defined as those adverse events reported in registration clinical trials with a frequency > 5%); (2) Determine the frequency of adverse reactions spontaneously notified by the patient (answering the question "have you noticed any discomfort related to the drug?"); (3) Evaluate the percentage of patients with an adequate BP in both groups; (4) Compare the patient's therapeutic compliance with every drug.

Adverse reactions were spontaneously reported by the patient or elicited using a 16-item checklist similar to the one used in the COHORT trial (Leonetti et al. 2002) that included those symptoms considered related to vasodilation and the most commonly adverse events reported during registration trials (see Appendix 1). Adequate BP control was defined as <140/90 mmHg in general population and <130/80 mmHg in people with diabetes (ADA 2005; ESH 2003). Since this study was aimed to reflect clinical practice, when BP control was not attained, the investigators could freely add more antihypertensive medication.

BP was measured with a standard mercury sphygmomanometer. Two measurements were taken, both in the sitting position and in the same arm with a 5-minute interval, and the average was used as the reference value. Patients underwent a complete physical examination, and they should have a complete blood test (hematology and biochemistry with a lipid profile) performed in the last three months before entering the study.

Treatment compliance was assessed through the Haynes-Sackett test (Sackett et al. 1991).

Statistical Analysis

The study sample calculation was based on the results of two previous studies (Leonetti et al. 2002; Romito et al. 2003). Based on the different proportions of edema detected in the first study (Leonetti et al. 2002) (9% lercanidipine vs. 19% amlodipine) and with the presence of an active control group with Nifedipine GITS, if we wanted to detect that difference we had to include a total of 650 patients (power = 90%, $\alpha = 0.05$). No dropouts were expected, as it was an observational study.

The primary variable of the study was evaluated through the frequency of ankle edema and other vasodilation-related adverse events according to the checklist used in the study. Secondary endpoints were

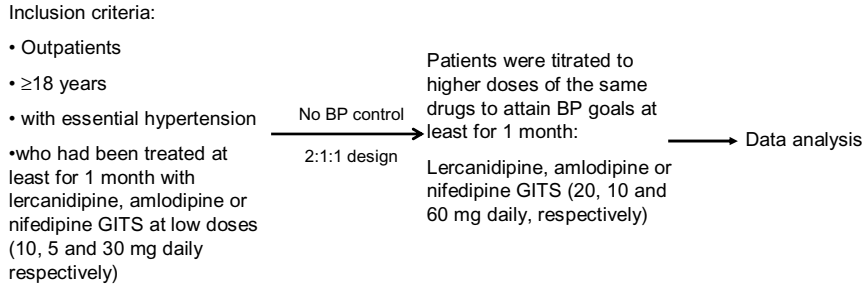

Figure 1 Study design.

Table 1 Clinical characteristics of study population.

	Global ($n = 650$)	Lercanidipine ($n = 446$)	Amlodipine/nifedipine ($n = 204$)	*P*
Age (years)	64.4 (11.1)	64.1 (10.9)	65.3 (11.4)	NS
Gender (male)	47%	48%	46%	NS
BMI (kg/m^2)	28.4 (4.3)	28.5 (4.3)	28 (4.2)	NS
Waist circumference (cm)	96.7 (15.5)	97 (15.7)	95.9 (15)	NS
Time since diagnosis (months)	63.7 (65.4)	62.2 (66)	66.9 (64.2)	NS
Smokers	27.3%	26.7%	28.4%	NS
Diabetes	26.1%	28.6%	20.7%	0.044
Hypercholesterolemia	47.7%	46.2%	51.1%	NS
Family history of hypertension	56.7%	54.9%	60.4%	NS

Data are expressed as means (standard deviation) or percentages. Low dose: treatment with dihydropyridines at low doses; High dose: treatment with dihydropyridines at high doses. NS: not significant ($P > 0.05$).

frequency of spontaneously adverse events notified by the patient, rates of BP control, and percentage of patients classified as good compliers according to the Haynes-Sacket test. Continuous variables were averaged and expressed as means ± standard deviation. Categorical items were expressed as percent frequency. 95% confidence intervals were provided when necessary. Differences between means of different parameters were compared by the Student *t*-test. Differences between percentages were compared with the Fisher's exact test. Categorical data were also analyzed with this test. A *P*-value < 0.05 was used as the level of statistical significance.

Computations for the statistical method were performed with the use of the SAS system. A logistic regression analysis was performed to determine what factors could influence the incidence of adverse events related to vasodilation (dependent variable). Clinical characteristics of study population, cardiovascular risk factors, target organ damage, associated clinical conditions, antihypertensive treatments, concomitant treatments, and biochemical parameters were included as independent variables in the logistic regression analysis.

Results

A total of 656 consecutive patients were included in the study. The number of evaluable subjects was 650 (99.1%) of whom 446 (68.6%) were taking lercanidipine and 204 (31.4%) amlodipine or nifedipine GITS ($n = 113$ and 91 respectively). Mean follow-up was 3.6 months. The clinical characteristics of the study population are shown in Table 1. The changes in BP and heart rate values during the study are shown in Table 2. The percentage of patients with an adequate BP control was 46.4% in the lercanidipine group versus 38.1% in the amlodipine/nifedipine group (P = NS). Concomitant antihypertensive therapy in both groups is shown in Table 3. There were more patients in the amlodipine/nifedipine group with concomitant antihypertensive medication than in the lercanidipine group (49% [42.1–55.9] vs. 38.3% [33.8–42.8] respectively, $P = 0.013$). Regarding the type of concomitant antihypertensive drugs, the only difference was a higher rate of angiotensin converting enzyme (ACE) inhibitors use in the amlodipine/nifedipine group (17.7 vs. 9%; $P = 0.002$). There were no significant differences between both groups in biochemical parameters as shown in Table 4.

Rates of signs and symptoms related to vasodilation were significantly higher ($P < 0.001$) in the amlodipine/nifedipine group (76.8%, CI 95% [70.7;82.9]) vs. lercanidipine group (60.8%, [56.1;65.5]) when the drugs were given at high doses. Corresponding figures for low doses were 41.2% [36.3;46.1] for lercanidipine and 58.8% [51.5;66.1] for amlodipine/nifedipine, the difference was statistically significant ($P < 0.001$). The difference in prevalence of vasodilation-related adverse

Table 2 Blood pressure and heart rates changes during the study.

	Global ($n = 650$)	Lercanidipine ($n = 446$)	Amlodipine/nifedipine* ($n = 204$)
SBP (low dose) mmHg	155.5 (13)	155.1 (13.8)	156.4 (11)
DBP (low dose) mmHg	90.3 (8.3)	90.4 (8.4)	90.1 (8.2)
HR (low dose) b.p.m.	78.3 (8,7)	78 (8.7)	78 (8.7)
SBP (high dose) mmHg	142.7 (12.4)	142.3 (12.2)	143.6 (12.7)
DBP (high dose) mmHg	82.3 (7.7)	82 (7.6)	83 (8)
HR (high dose) b.p.m.	76.5 (8.3)	76.4 (8.4)	76.7 (8.2)

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
*SBP and DBP: $P < 0.05$ in lercanidpine and amlodipine/nifedipine groups versus low dose; $P =$ NS between both groups. HR: $P =$ NS.

Table 3 Concomitant antihypertensive therapy.

	Global ($n = 650$)	Lercanidipine ($n = 446$)	Amlodipine/nifedipine ($n = 204$)	*p*
ARB	15.2%	14.6%	16.7%	NS
ACE inhibitors	11.7%	9%	17.7%	0.002
Diuretics	21.4%	21.3%	21.6%	NS
Betablockers	5.4%	4.5%	7.4%	NS
α blockers	2.6%	2.7%	2.5%	NS
Other	1.2%	1.1%	1.5%	NS

ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme.

Table 4 Biochemical parameters in overall study population, lercanidipine and amlodipine/nifedipine subgroups.

	Global ($n = 650$)	Lercanidipine ($n = 446$)	Amlodipine/nifedipine ($n = 204$)	*P*
Glucose (mg/dL)	112 (37.1)	113.1 (41.4)	109.5 (25.7)	NS
Creatinine (mg/dL)	1.0 (0.4)	1.0 (0.4)	1.0 (0.3)	NS
Sodium (mEq/L)	140 (4.7)	139.2 (5.0)	140.2 (4.1)	NS
Potassium (mEq/L)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)	NS
Urate (mg/dL)	5.8 (1.4)	5.8 (1.4)	5.9 (1.5)	NS
Cholesterol (mg/dL)	216 (36.9)	217 (36.4)	214 (38)	NS
c-HDL (mg/dL)	53.7 (17)	54.6 (18)	51.9 (14.8)	NS
c-LDL (mg/dL)	136.4 (31.2)	136.5 (31.1)	136.2 (31.4)	NS
Triglycerides (mg/dL)	150.3 (68.9)	149.3 (58.2)	152.4 (87.8)	NS

Values are expressed as means (standard deviation); NS, not significant ($P > 0.05$).
HDL, high-density lipoprotein. LDL, low-density lipoprotein.

reactions between high and low doses in every group was also significant (60.8 vs. 41.2% for lercanidipine and 76.8 vs. 58.8% for amlodipine/nifedipine, both $P < 0.001$). Table 5 shows the distribution between groups of drug related signs and symptoms according to the checklist.

Classification of the severity of adverse reactions was as follows: 74.5% [69.1–79.9] mild, 22.7% [17.5–27.9] moderate, and 2.8% [0.7–4.9] severe in the lercanidipine group versus 64% [56–72] mild, 32.4% [24.6–40.2] moderate, and 3.6% [0.5–6.7] severe in the amlodipine/nifedipine group. Differences between groups were statistically significant for mild ($P = 0.035$) and moderate adverse events ($P = 0.040$), but not for severe ones. With regard to adverse events spontaneously notified by the patients, there were no statistically significant differences between both groups of DHP-treated patients. Around 2.7% of patients from lercanidipine group and 6.1% from amlodipine/nifedipine group droppedout during the first month of the high dose treatment ($P =$ NS).

According to the Haynes-Sackett test, the percentage of patients considered good compliers was similar in both groups (93.9% lercanidipine vs. 93.7% in amlodipine/nifedipine, $P =$ NS). Concerning the changes in antihypertensive treatment made by the investigators, in 91.2% of patients in the lercanidipine group the treatment was maintained, whereas in the amlodipine/nifedipine group only 56.1% did not change their treatment regimen ($P < 0.001$). Table 6 shows the most frequent changes in the therapeutic regimen made by the investigators. The most frequent modification performed

Table 5 Distribution of signs and symptoms according to the checklist with dihydropyridines given at high doses.

Signs/symptoms	Global (%) ($n = 650$)	Lercanidipine (%) ($n = 446$)	Amlodipine/nifedipine (%) ($n = 204$)	*P*-value
Leg edema	45.1	39.7	57.3	<0.001
Swelling	31.4	25.7	44.1	<0.001
Dizziness	13.8	12.4	16.9	NS
Blurred vision	7.6	6.7	9.6	NS
Flushes	32.2	26.5	45.0	<0.001
Headache	30.4	25.4	41.6	<0.001
Palpitations	13.6	10.9	19.7	0.006
Fatigue	16.9	13.7	24.2	0.003
Thoracic pain	4.5	4.5	4.5	NS
Dyspnea	8.4	6.8	11.9	0.049
Pyrosis	11.8	9.5	16.9	0.016
Constipation/diarrhea	13.2	10.7	18.6	0.011
Skin rush	7.4	4.6	13.5	<0.001
Sexual dysfunction	10.9	9	15.2	0.030
Thoracic swelling	1.9	1.8	2.3	NS
Gum swelling	2.5	2.0	3.4	NS

NS, not significant ($P > 0.05$).

Table 6 Changes in antihypertensive regimen made by the investigators.

	Global $N = 119$	Lercanidipine $N = 37$	Amlodipine/nifedipine $N = 82$	*P*-value
Add a new agent	44.5%	75.7%	30.5%	<0.001
Reduce dose of CCB	16%	27%	11%	0.033
Withdraw the CCB	5%	2.7%	6.1%	NS
Change of CCB	47.1%	-	68.3%	<0.001

CCB, calcium channel blocker; NS, not significant.

in lercanidipine group was the addition of a new agent (75.7%), while in amlodipine/nifedipine group the change to other CCB (68.3%).

A logistic regression model was performed to check which factors could influence the appearance of adverse events related to vasodilation. The following variables were found to be significant: male sex (Odds ratio 2.072, CI 95% [1.395–3.077]), sedentary life (1.608, [1.085–2.384]), antecedents of cardiac (6.102 [2.668–13.954]), or gastrointestinal diseases (1.965 [1.157–3.335]). Patients in the lercanidipine group had a lower risk of having these adverse reactions (odds ratio 0.436 [0.278–0.684]).

Discussion

The main objective in the treatment of hypertension is to achieve an adequate BP control and to reduce the global cardiovascular risk of the hypertensive patient. Pharmacological treatment of hypertension is almost always lifelong lasting. Thus, an antihypertensive drug should not only be able to effectively reduce BP but also have a good tolerability profile to avoid compliance reduction. Dihydropyridines have shown to be effective antihypertensive drugs in several clinical trials, but its use has been sometimes limited due to their side effects, particularly ankle edema. However, not all the compounds of this antihypertensive class share the same adverse event risk profile. In this respect, this new DHP appears to be associated with lower rates of drug-related side effects.

The main objective of this study was to compare tolerability of high doses of lercanidipine versus high doses of other DHP (amlodipine/nifedipine GITS) in common clinical practice. The main variable was adverse events related to vasodilation. Incidence of these side effects was significantly higher in the amlodipine/nifedipine group compared to lercanidipine. This difference could not be explained by a greater BP lowering effect of the amlodipine/nifedipine group, because rates of BP control were similar in both groups. When these drugs were given at low doses this difference was still significant. Concomitant antihypertensive medication was not related to this difference either, because it was not clinically different in both groups. In fact, the rate of use of ACE inhibitors, drugs that could alleviate lower limb edema induced by DHP (Weir et al. 2001), was higher in the amlodipine/nifedipine group. The exact mechanism of this attenuation of dependent fluid extravasation by the ACE inhibitors is not known. The main hypothesis is that they could counterbalance the rise in capillary pressure secondary to the more effective inhibition of precapillary

Table 7 Summary table

What is known about topic	What this study adds
• The poor control of hypertension may be partially due to the low treatment compliance of the patients	• In daily clinical practice, treatment with lercanidipine at high doses is associated with a lower rate of adverse reactions related to vasodilation compared to high doses of amlodipine or nifedipine GITS
• Some factors that have been involved in this poor compliance are adverse events related to antihypertensive drugs, lifelong treatment and polymedication	• Blood pressure control (< 140/90 mmHg or <130/80 for diabetics) and type of concomitant antihypertensive medications were similar in both groups
• Lercanidipine is generally well tolerated during monotherapy in patients with mild-to-moderate hypertension	

resistance by the DHP through a preferential venodilatation effect at the microcirculatory level.

For every group, the increase of dose was associated with a higher incidence of signs and symptoms related to vasodilation suggesting that these side effects are dose dependent. Incidence of leg edema was high in both groups (39.7% in lercanidipine vs. 57.1% in amlodipine/nifedipine group) and similar to that reported in other studies (Leonetti et al. 2002). It is noticeable that the presence of leg edema was elicited by using the symptom and signs check list. Thus, it is most likely that a simple heaviness could be interpreted by the patient as ankle edema, what could explain the high incidence of that side effect in both groups.

Vasodilatory edema related to DHP is probably due to an increase in intracapillary hydrostatic pressure that causes fluid filtration from the vascular space to the interstitium. It has been related to an arteriolar dilation that, as a consequence of reflex sympathetic activation, is not accompanied by adequate postcapillary vasodilation (Angelico et al. 1999; Lund-Johansen et al. 2003). Lercanidipine has shown different effects on plasma norepinephrine levels and a lower sympathetic activation compared with other DHP (Fogari et al. 2003; Grassi et al. 1998;), what could, at least in part, explain the lower rate of leg edema observed with this drug when compared to amlodipine or nifedipine. These results are in concordance with those previously described in other clinical trials (Agrawal et al. 2006; Barrios et al. 2002; Barrios et al. 2006a; Barrios et al. 2006b; James et al. 2002; Leonetti et al. 2002; Millar-Craig et al. 2003; Viviani 2002; Pedrinelli et al. 2003; Romito et al. 2003). Nevertheless, in most of these studies, the dose of lercanidipine initially used was 10 mg per day (considered low dose in our study) and it was titrated to 20 mg only if necessary. Thus, most of the patients in these studies were treated with low doses of lercanidipine. Remarkably, the incidence of fatigue and sexual dysfunction was also significantly lowerin lercanidipine group. This result is concordant with others (Borghi et al. 2003).

Regarding the severity of the adverse events, we did not find a statistically significant difference between groups in severe adverse events. The incidence was quite low in both groups (around 3%) suggesting a good safety profile of these drugs. In relation to this, treatment compliance (with the inherent limitations of the test used for its assessment) was very good and similar in both groups (around 94%). Changes in hypertensive medication were more frequent in the amlodipine/nifedipine group. As far as BP values were comparable in both groups, these changes were probably mostly related to the higher incidence of adverse events in the amlodipine/nifedipine group, as shown in Table 5. The most common action in the lercanidipine group was to add a new drug whereas in the amlodipine/nifedipine group was to change the CCB. Switching from a CCB to another because of adverse events is common in daily practice. It is also in accordance with the information derived from other studies, where patients treated with other CCB who experienced typical DHP-related adverse events were switched from that treatment to lercanidipine with a resulting significant reduction of side effects (Borghi et al. 2003; Lund-Johansen et al. 2003; Beckey et al. 2007).

In our study the variables that could influence the appearance of adverse events related to vasodilation were male sex, contrary to what has been previously published in the literature (Cherubini et al. 2003), sedentary life (probably due to gravitational factors), and antecedents of cardiac or gastrointestinal disease (probably due to the intrinsic higher risk of some cardiac or gastrointestinal diseases for the development of leg edema). Treatment with lercanidipine was a protective factor compared to the use of amlodipine or nifedipine GITS.

This is an observational study with its characteristic design and results limitations. This methodology has its limitations since it reduces the level of control that can be exercised to reduce variation and bias (e.g., random sampling). However, the large number of patients included and the nature of the endpoints being measured, minimizes this theoretical limitation. The information derived from this kind of studies is very useful and complementary to the one obtained from the randomized controlled trials. Observational studies include more often older patients with a higher comorbidity what, in terms of drug

tolerability, could reflect the "real-world" clinical scenario better than randomized controlled trial. The method used to evaluate compliance is the self-communicated interview as indicated by Haynes-Sackett. Despite the limitations of this test, it has been shown that this test can determine adequately the treatment compliance in clinical practice (Gil et al. 2003; Roth and Ivey 2005). Table 7 summarizes the key points of our study.

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Conflict of Interest

The authors have no conflict of interest.

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APPENDIX 1. Symptoms and signs checklist

	High dose DHP				Low dose DHP			
Lower limb edema	0	1	2	3	0	1	2	3
Lower limb swelling, numbness, tingling	0	1	2	3	0	1	2	3
Dizziness	0	1	2	3	0	1	2	3
Sight disturbances	0	1	2	3	0	1	2	3
Flushing/heat sensation	0	1	2	3	0	1	2	3
Headache	0	1	2	3	0	1	2	3
Tachycardia/palpitation	0	1	2	3	0	1	2	3
Fatigue/weakness	0	1	2	3	0	1	2	3
Chest pain	0	1	2	3	0	1	2	3
Dyspnea	0	1	2	3	0	1	2	3
Pyrosis	0	1	2	3	0	1	2	3
Constipation or diarrhea	0	1	2	3	0	1	2	3
Skin rush	0	1	2	3	0	1	2	3
Sexual dysfunction	0	1	2	3	0	1	2	3
Breast swelling/gynecomastia	0	1	2	3	0	1	2	3
Gingival swelling or bleeding	0	1	2	3	0	1	2	3

0 = Absent.

1 = Mild (occasionally present, does not affect daily life activities).

2 = Moderate (often present, affects daily life activities).

3 = Severe (unable to carry out daily life activities).

DHP: dihydropyridines.