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Azelnidipine

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Contents

Abstract

▲ Azelnidipine is a new dihydropyridine calcium channel antagonist with selectivity for L-type calcium channels that has recently been approved in Japan for the treatment of patients with hypertension.

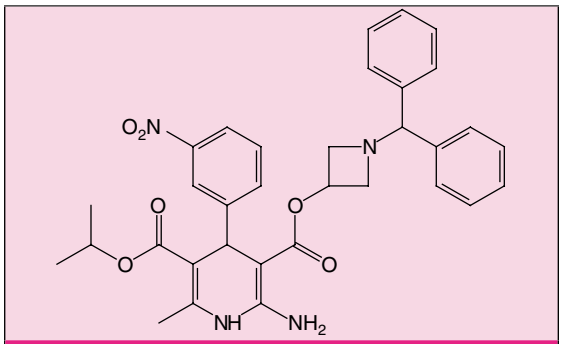
▲ Results from clinical trials showed that, in 95 patients with mild-to-moderate hypertension, long-term treatment with azelnidipine effectively controls blood pressure (BP). The mean reduction from baseline in sitting systolic/diastolic BP after 1 year of treatment was 27.8/16.6mm Hg.

▲ Among 172 patients with uncontrolled hypertension receiving non-calcium channel antagonist antihypertensive agents, the addition of azelnidipine therapy significantly reduced mean BP in a non-comparative, 1-year study (a reduction from 165.7/95.4mm Hg at baseline to 138.2/79.9mm Hg at study end).

▲ The antihypertensive efficacy of azelnidipine in patients with mild-to-moderate hypertension was shown to be similar to that of amlodipine or nitrendipine in randomised, double-blind studies. Azelnidipine and amlodipine controlled 24-hour BP to a similar extent.

▲ Azelnidipine is generally well tolerated; vasodilator adverse events such as as headache and hot facial flushes account for most of the adverse events. Its use is not associated with reflex tachycardia.

Features and properties of azelnidipine (Calblock®)	
Indications	
Hypertension	
Mechanism of action	
Inhibition of calcium influx through L-type channels in cell membranes	
Dosage and administration	
Recommended dosage	8–16 mg/day
Route of administration	Oral
Frequency of administration	Once daily after a meal
Steady-state pharmacokinetics in healthy volunteers (8mg once daily for 7 days)	
Peak plasma concentration	14.7 ng/mL
Area under the plasma concentration-time curve	81.6 ng • h/mL
Time to peak plasma concentration	2.2h
Terminal elimination half-life	19.2h
Adverse events	
Most frequent	Headache, hot facial flushes, light-headedness



Azelnidipine.

Chronically elevated blood pressure (BP) is associated with an increased risk of cardiovascular morbidity and mortality, and with end-stage renal failure.[1] The minimisation of cardiovascular risk by controlling BP is a primary goal of the treatment of hypertension.[1-3] Calcium channel antagonists (calcium channel blockers) are widely used for the treatment of hypertension, and their antihypertensive efficacy is similar to that of β-blockers (β-adrenoceptor antagonists), ACE inhibitors and thiazide diuretics.[4]

Azelnidipine (Calblock®[1]) is a new dihydropyridine calcium channel antagonist that, like other members of this drug class, is selective for L-type calcium channels. It is composed of a racemic mixture containing a 1:1 ratio of the active *R*-enantiomer and the inactive *S*-enantiomer, and is used for once-daily oral administration in the treatment of patients with hypertension.[5]

1. Pharmacodynamic Profile

Receptor-Binding and *In Vitro* Properties

- Azelnidipine reversibly blocks voltage-dependent Ca^{2+} influx through L-type calcium channels in the cell membrane.[6] *In vitro* studies showed that azelnidipine competitively inhibits the binding of radiolabelled nitrendipine in porcine heart membrane fractions, with a concentration required for 50% inhibition (IC_{50}) of 3.1 nmol/L and an apparent dissociation constant (K_i) of 2.1 nmol/L. In comparison, amlodipine and nicardipine had IC_{50}s of 180 and 0.23 nmol/L, and K_is of 120 and 0.15 nmol/L.[6]
- *In vitro* studies in isolated rat aortic strips have shown that, consistent with its high lipophilicity, azelnidipine has a long duration of action.[7] The maximal inhibitory effect of azelnidipine 1–10 nmol/L on potassium-induced contractions was not reached within the 6 hours of incubation. In contrast, the inhibitory effect of nicardipine 0.3 or 1 nmol/L plateaued after about 1.5 hours. Furthermore, the inhibitory effects of azelnidipine 3–30 nmol/L (tissues exposed to drug for 40 minutes) continued to increase during the 4 hours after washout, whereas the effects of nicardipine decreased gradually upon washout, with no inhibitory effects apparent after 4 hours.[7]

Haemodynamic Effects

Animal Studies

- A single dose of azelnidipine 0.3, 1 or 3 mg/kg administered by gavage to conscious spontaneously hypertensive rats (SHRs) produced dose-dependent reductions in mean arterial pressure.[7] The reduction in arterial pressure was gradual, reaching a nadir approximately 6 hours after administration and, at the dose of 3 mg/kg, was sustained for approximately 20 hours post-administration. The maximal reduction in mean arterial pressure was approximately 10%, 20% and 35% in the 0.3, 1 and 3 mg/kg groups, respectively. The drug had a small effect on heart rate, increasing it by a maximum of 25% immediately after administration.[7] A similar effect on mean arterial pressure and heart rate was seen in conscious hypertensive dogs after oral administration of a single dose of azelnidipine 1 or 3 mg/kg.[8]
- Administration of oral azelnidipine 1 or 3 mg/kg/day for 15 weeks produced a sustained reduction in systolic BP (SBP) in SHRs without the development of tolerance; at the end of treatment, SBP was reduced from baseline by 19 and 43mm Hg in the two groups, respectively. Furthermore, cardiac output

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

increased (by ≈16% and ≈22%, respectively, compared with controls; $p < 0.05$ for higher dosage), total peripheral resistance decreased (by ≈26% and 29%; $p < 0.05$ for both) and cardiac hypertrophy was prevented in both treatment groups.[9]

- After 15 weeks of oral azelnidipine 3 mg/kg in SHRs, blood flow to the kidneys, brain and spleen was significantly (all $p < 0.05$) higher than in control animals.[9] Blood flow to the heart, liver, stomach, small and large intestines, testes and skeletal muscle was not significantly different to that in control animals.
- Compared with intravenous amlodipine 0.03–3 mg/kg, intravenous azelnidipine 0.03–1 mg/kg had a greater intrinsic negative chronotropic action and less baroreceptor reflex activation in anaesthetised dogs because of the more gradual BP-lowering effects of azelnidipine.[10] Furthermore, the PQ interval was not prolonged in anaesthetised dogs treated with azelnidipine 0.03–1 mg/kg compared with vehicle-treated dogs; although amlodipine 0.03–1 mg/kg did not increase the PQ interval, the 3 mg/kg dosage increased it by approximately 20 msec ($p < 0.05$ vs vehicle).[10]

Studies in Patients

- In a randomised, double-blind, placebo-controlled, crossover study in ten patients with mild essential hypertension, azelnidipine 8 mg/day for 4 weeks significantly decreased sitting SBP/diastolic BP (sSBP/sDBP) from baseline (from 158/97mm Hg to 145/90mm Hg, $p < 0.01$) without significantly affecting heart rate, cardiac output, systemic vascular resistance or plasma levels of norepinephrine (noradrenaline), epinephrine (adrenaline) or aldosterone.[11] Similar effects were seen during exercise; azelnidipine significantly ($p < 0.05$) lowered BP without affecting the exercised-induced increases in heart rate, cardiac output or plasma neurohormonal levels, or the exercise-induced decrease in systemic vascular resistance. The drug did, however, augment the exercise-induced increase in left ventricular fractional shortening.[11]
- Azelnidipine 8–16mg administered once daily in the morning significantly reduces BP over 24 hours, as demonstrated with 24-hour ambulatory BP monitoring.[12-15] In two studies,[14,15] SBP/DBP was significantly reduced during the night-time ($p < 0.01$ vs baseline) and during the daytime ($p < 0.001$ vs baseline). In the other two studies,[12,13] although DBP reductions were generally not significant during the night, SBP was significantly ($p < 0.05$) reduced throughout the night in one of the studies;[13] the trough-to-peak ratios in these two studies were 58%[13] and 62%.[12]
- Azelnidipine 8–16mg once daily for 2–10 weeks effectively reduced BP in 27 patients with either renal dysfunction and hypertension (n = 7) or renal parenchymal disease and hypertension (n = 20); mean pretreatment sSBP/sDBP was 170/104mm Hg.[16] The mean reduction from baseline in BP in patients with renal dysfunction was 24/18mm Hg (mean sSBP/sDBP 147/86mm Hg at study end, $p < 0.01$ vs baseline). In patients with renal parenchymal disease, the mean reduction in BP was 21/16mm Hg (mean sSBP/sDBP 149/87mm Hg at study end, $p < 0.001$ vs baseline).[16]

End-Organ Protection

Animal Studies

- Preclinical data indicate azelnidipine may protect the kidneys in SHRs[9,17-20] and have beneficial effects on the ischaemic myocardium in dogs.[21]
- Oral azelnidipine 1 mg/kg produced a 2-fold increase in urine flow and a 9-fold increase in sodium excretion in conscious SHRs.[18] The diuretic and natriuretic effects of the drug were gradual, becoming apparent in the second hour after administration and were sustained during hours 3 and 4. Azelnidipine also caused a significant increase from baseline in glomerular filtration rate (GFR; by ≈39%, $p < 0.05$) but did not affect renal plasma flow. When the drug was administered intrarenally at doses of 0.5, 1 and 2 μg/kg/min for 20 minutes in normotensive male Munich Wistar rats, urine flow and sodium excretion increased dose dependently, but the GFR and renal plasma flow were unaffected.[18]
- In SHRs with puromycin aminonucleoside-induced renal dysfunction (GFR ≈43% lower than in

control SHRs), a single oral 3 mg/kg dose of azelnidipine significantly ($p < 0.05$) increased natriuresis between 2 and 5 hours after administration; azelnidipine 10 mg/kg had no effect on sodium excretion.[20] The GFR was unaffected by azelnidipine 3 mg/kg, but the 10 mg/kg dose decreased it significantly during the second hour after administration (by 32%, $p < 0.05$ vs vehicle-treated SHR controls).

• Chronic administration of oral azelnidipine significantly reduced arterial and glomerular injury in SHR kidneys.[19] The incidences of renal arterial intimal proliferation (5.4% vs 34.1%, $p < 0.05$), glomerular sclerosis (22.3% vs 42.5%, $p < 0.05$) and pericapsular fibrous thickening (11.8% vs 46.3%, $p < 0.01$) were all significantly lower in SHRs after 15 weeks' oral administration of azelnidipine 3 mg/kg/day than after administration of vehicle.[19]

• Combination therapy with azelnidipine plus the ACE inhibitor temocapril provided better renoprotection than monotherapy with either agent.[17] In SHRs that had undergone subtotal (five-sixths) renal ablation, treatment with oral azelnidipine 3 mg/kg/day plus temocapril 10 mg/kg/day for 12 weeks significantly reduced mean urinary albumin excretion and the extent of glomerular sclerosis compared with the same dosage of azelnidipine ($p < 0.01$ and 0.05) or temocapril ($p < 0.05$ and 0.001). Both drugs when administered alone also provided renal protection greater than that in vehicle-treated controls.[17]

• Pretreatment with azelnidipine improved myocardial contractile dysfunction in dogs during reperfusion after ischaemia.[21] Intravenous azelnidipine 0.1 or 0.3 mg/kg produced a significant ($p < 0.05$) enhancement of the recovery of the myocardial segment shortening during reperfusion, compared with that in vehicle-treated dogs.

Studies in Patients

• In six hypertensive patients with normal renal function, oral azelnidipine 8–16mg once daily for 12 weeks significantly increased renal plasma flow (by 11.2%, $p < 0.05$) and renal blood flow (by 9.5%, $p < 0.05$) compared with baseline.[22] The GFR was slightly, but not statistically significantly, increased (by 8.9%), the filtration fraction remained unchanged, and renovascular resistance significantly decreased (by 19%, $p < 0.01$). Azelnidipine therapy had no effect on plasma levels of renin, aldosterone, angiotensin I or angiotensin II in these patients.[22]

Antiatherosclerotic Effects

• Azelnidipine 8–16mg once daily for 12 weeks to 1 year had a mild antiatherosclerotic effect in 19 patients with mild-to-moderate hypertension.[23] Although azelnidipine significantly reduced the carotid intimal-medial wall thickness (by 21.6% after 1 year, $p < 0.01$ vs baseline) and serum lipid peroxide levels (by 43.7% after 12 weeks, $p < 0.01$ vs baseline), it had no effect on serum lipids or serum superoxide dismutase activity.

2. Pharmacokinetic Profile

• Oral azelnidipine shows rapid, dose-dependent absorption. After single-dose oral administration of azelnidipine 5–15mg to healthy, fasting adult volunteers, mean peak plasma concentrations (C_{max}) of 3.0–13.1 ng/mL occurred 2.3–2.7 hours (t_{max}) postdose; the mean area under the plasma concentration-time curve from zero to infinity (AUC_∞) was 27.5–135.8 ng • h/mL.[24] After multiple-dose administration of azelnidipine 8 mg/day for 7 days, mean C_{max} and AUC_{24h} values were 14.7 ng/mL and 81.6 ng • h/mL; t_{max} on day 7 was 2.2 hours.[25] Steady-state plasma concentrations of azelnidipine were achieved after day 2. *In vitro* data suggest that azelnidipine is extensively bound to plasma lipoproteins (≈90%).[26]

• Like most calcium channel antagonists, azelnidipine undergoes extensive first-pass hepatic metabolism.[5] *In vivo* studies in rats and dogs have shown that no parent drug is detected in either the urine or the faeces.[5] Metabolism is thought to be mediated primarily by cytochrome P450 (CYP) 3A4.[26] The mean terminal elimination half-life ($t_{1/2}\beta$) of azelnidipine was approximately 14–20 hours following single oral 5–15mg doses to healthy volunteers;[24] at steady state, the $t_{1/2}\beta$ was 19.2 hours after administration of azelnidipine 8 mg/day for 7 days.[25]

• Administration of azelnidipine with food increased the extent but not the rate of absorption. When a single oral 10mg dose of azelnidipine was administered after a meal, mean C_{max} was 2.6-fold higher than values obtained in the fasted state (18.5 vs 7.1 ng/mL, $p < 0.05$); although mean AUC_{∞} was 1.5-fold higher, the difference was not statistically significant (115.4 vs 79.4 ng • h/mL).[27] Mean t_{max} (2.3 vs 2.7h) and $t_{1/2}\beta$ (16.2 vs 20.9h) were not statistically significantly different in the fed and fasted state.[27] Administration of azelnidipine after a meal is recommended by the manufacturer (section 5).[26]

• The pharmacokinetics of azelnidipine in patients with hypertension appear to be similar to those in healthy volunteers.[26] After oral administration of a single 8mg dose to six patients with mild-to-moderate hypertension, a mean C_{max} of 9.4 ng/mL was reached 3.7 hours postdose; the AUC_{24h} was 66.5 ng • h/mL.[26]

• In five elderly patients (aged 65–84 years) with hypertension, mean C_{max} and AUC_{24h} values of azelnidipine after a single 8mg dose administered after a meal were 15.8 ng/mL and 107 ng • h/mL.[28] After repeat dosing of 8 mg/day for 7 days, corresponding values were 25.7 ng/mL and 242.8 ng • h/mL ($p < 0.05$ vs day 1 for both). Systemic clearance was also significantly reduced after 7 days compared with a single dose (640 vs 1321 mL/min, $p < 0.05$).

• In hypertensive patients with renal dysfunction, steady-state plasma concentrations of azelnidipine were approximately 2-fold higher than those in healthy volunteers ($p < 0.01$).[29]

• Since azelnidipine is metabolised by CYP3A4, it has the potential for interactions with other drugs or compounds that are substrates for this enzyme. Azelnidipine C_{max} and AUC_{12h} values were 1.6- and 2.8-times higher after concomitant administration of itraconazole 50mg and azelnidipine 8mg than with azelnidipine alone.[26]

3. Therapeutic Efficacy

The antihypertensive efficacy of oral azelnidipine has been evaluated in patients with mild-to-moderate hypertension in several dose-response studies,[30-32] a long-term monotherapy study[33] and was compared with that of oral amlodipine in a 6-week, randomised, double-blind study,[15] and oral nitrendipine in a 12-week, randomised, double-blind, multicentre study.[34] The drug has also been evaluated in patients with uncontrolled hypertension while receiving non-calcium channel antagonist antihypertensive agents.[35] The primary endpoint in all studies was mean reduction from baseline in sSBP/sDBP; patients were considered to have responded to treatment if sSBP/sDBP was reduced by ≥20/10mm Hg or had decreased to ≤149/89mm Hg (considered to be normalised sitting BP).

Short-Term Studies

• Several dose-response studies in patients with mild-to-moderate hypertension have indicated that the effective therapeutic range of azelnidipine is 8–16mg once daily.[30-32]

• In the largest dose-response study (n = 222),[32] which was of double-blind, multicentre design, patients received azelnidipine 6 mg/day for 6 weeks followed by non-forced titration to 12 mg/day for 4 weeks (low-dose group; dosage referred to as 6–12 mg/day) or azelnidipine 8 mg/day for 6 weeks followed by non-forced titration to 16 mg/day (high-dose group; dosage referred to as 8–16 mg/day). Mean sSBP/sDBP was significantly ($p < 0.001$) reduced from baseline by week 2 in both treatment groups, and continued to decrease gradually until study end; there were no significant between-treatment group differences in BP reductions. At week 10, 68.2% and 75.0% of azelnidipine 6–12 mg/day or 8–16 mg/day recipients had responded to treatment.[32]

• Azelnidipine 16 mg/day for 6 weeks reduced sSBP/sDBP and controlled 24-hour BP (assessed by ambulatory BP monitoring) to a similar extent as amlodipine 5 mg/day in a randomised, double-blind study in 45 patients with mild-to-moderate hypertension.[15] At week 6, sSBP/sDBP reductions from baseline were similar in azelnidipine and amlodipine recipients (mean reductions of 13/8 vs 13/7mm Hg; baseline BP was ≈154/97mm Hg). There were

no significant between-group differences in 24-hour BP control (figure 1); however, heart rate was significantly ($p < 0.001$) lower in the azelnidipine group than in the amlodipine group at study end (see figure 1 and section 4). The trough-to-peak ratios for azelnidipine and amlodipine in this study were 63.6% and 46.2%.

- Azelnidipine was as effective as nitrendipine in reducing BP over the 12-week treatment period in a randomised, double-blind trial.[34] After a 4-week placebo run-in, 408 patients (mean age 58 years) with mild-to-moderate hypertension (mean sSBP/sDBP ≈169/101mm Hg) received azelnidipine 8mg (n = 208) or nitrendipine 5mg (n = 200) once daily for 4 weeks followed by non-forced titration to azelnidipine 16mg or nitrendipine 10mg for 8 weeks.

- A similar proportion of patients in both treatment groups had responded to treatment by week 12 in this trial; 72.6% and 74.5% of azelnidipine or nitrendipine recipients had an sSBP/sDBP reduction of ≥20/10mm Hg.[34] The mean reduction from baseline in sSBP/sDBP at week 12 in the azelnidipine group was 24.7/14.7mm Hg ($p = 0.001$ vs baseline), compared with 25.5/14.8mm Hg ($p = 0.001$ vs baseline) in the nitrendipine group. BP was normalised in 51.0% and 54.0% of azelnidipine or nitrendipine recipients.

- Mean sSBP/sDBP had decreased significantly ($p < 0.001$) from baseline after 2 weeks of treatment in the azelnidipine and nitrendipine groups, and continued to decrease, albeit more slowly, throughout the duration of the study.[34]

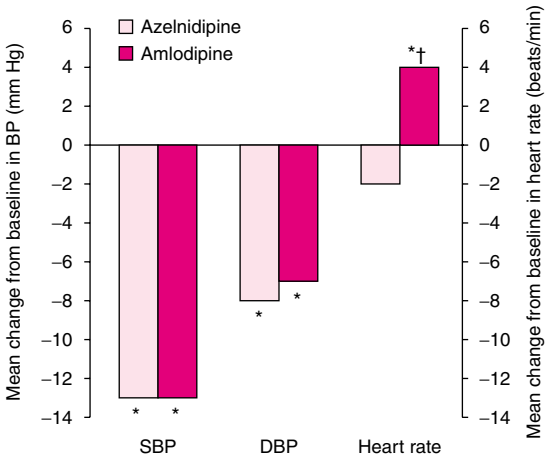


Fig. 1. The effects of azelnidipine and amlodipine on 24-hour blood pressure (BP) control and on heart rate after 6 weeks of treatment. Patients with mild-to-moderate hypertension (baseline seated systolic/diastolic BP [sSBP/sDBP] ≈154/97mm Hg) were randomised to receive once-daily azelnidipine 16mg (n = 22) or amlodipine 5 mg (n = 23) for 6 weeks in a double-blind study.[15] Mean 24-hour BP and heart rate, calculated from ambulatory BP and pulse measurements taken every 30 minutes for 24 hours after 6 weeks of treatment, were compared with corresponding baseline measurements. * $p < 0.001$ vs baseline; † $p < 0.001$ vs azelnidipine.

Long-Term Studies

- The efficacy of azelnidipine monotherapy was maintained for 1 year in 95 patients with mild-to-moderate hypertension.[33] After a 4-week placebo run-in, 95 patients with mild-to-moderate hypertension (mean sSBP/sDBP 168.0/100.2mm Hg) received azelnidipine 8 or 16 mg/day (dose escalation by non-forced titration) for 1 year. BP decreased significantly ($p < 0.001$) from baseline after 2 weeks and was maintained for the duration of the study. The mean reduction from baseline in sSBP/sDBP after 1 year of treatment was 27.8/16.6mm Hg (mean sSBP/sDBP 140.2/83.6mm Hg at study end). Mean heart rate had decreased by 2.2 beats/min ($p < 0.05$ vs baseline) after 1 year of treatment.[33]

- After 6 months' therapy, 86.8% of patients had responded to treatment, with a similar response rate (87.4%) at 1 year.[33] Additionally, the proportion of patients aged ≥65 years (n = 26) who responded to treatment after 1 year was similar to the proportion of responders aged <65 years (n = 69) [84.6% vs 88.4%].[33]

- Among patients with uncontrolled mild-to-moderate hypertension while receiving non-calcium channel antagonist antihypertensive agents (n = 172, mean sSBP/sDBP 165.7/95.4mm Hg), the addition of azelnidipine 8 or 16 mg/day therapy (using the non-forced titration method) significantly ($p < 0.001$) reduced BP during the first month and maintained it for 1 year in a noncomparative study.[35] In the overall population, the mean reduction from baseline in sSBP/sDBP after 1 year of treatment was 27.5/15.5mm Hg (mean sSBP/sDBP 138.2/79.9mm

Hg at study end); 76.7% of all patients responded to treatment. Mean heart rate had decreased by 1.4 beats/min ($p < 0.05$ vs baseline) after 1 year of treatment.[35]

- The proportion of patients who responded to treatment was similar in subgroups of patients stratified by the number of concomitant antihypertensive drugs they were taking. Concomitant antihypertensive medication included ACE inhibitors, β-blockers, α-adrenoceptor antagonists (α-blockers), diuretics and CNS depressants (specific agents and dosages were not reported). Patients were taking one (n = 141), two (n = 25) or three (n = 6) concomitant antihypertensive drugs.[35] Moreover, patients aged ≥65 years (n = 99) responded to treatment just as effectively as younger patients (75.3% vs 77.8%).

4. Tolerability

- Azelnidipine was generally well tolerated in clinical trials,[15,30-35] with most treatment-emergent adverse events related to vasodilation; the drug is not associated with reflex tachycardia. According to the manufacturer's prescribing information,[26] the most common adverse events in clinical trials (n = 1103) were headache (1.1%), hot facial flushes (0.5%) and light-headedness (0.5%); there were no reports of peripheral oedema. In a pooled analysis of data from ten studies involving 765 patients with hypertension who received azelnidipine 8–16 mg/day, 16.6% of patients reported treatment-related adverse events; all of these adverse events were considered either mild (78%) or moderate (22%) in severity.[36]
- In the 12-week, double-blind comparison with nitrendipine (section 3), adverse events were reported in significantly fewer azelnidipine 8–16 mg/day recipients than nitrendipine 5–10 mg/day recipients (10.6% vs 24.5%, $p < 0.001$).[34] Azelnidipine was associated with significantly fewer CNS-related adverse events than nitrendipine (5.8% vs 14.5%, $p < 0.01$), particularly headache (2.9% vs 10.5%) and light-headedness (0% vs 2.5%) [statistical analyses were not performed for individual adverse-event rates]. General adverse events were also experienced by significantly fewer azelnidipine recipients (2.4% vs 12.0%, $p < 0.001$), particularly hot facial flushes (0.5% vs 6.5%). Furthermore, heart rate did not significantly increase from baseline during treatment with either drug, and there were no significant differences in heart rate between treatment groups. In this study, 2.9% and 4.5% of azelnidipine or nitrendipine recipients withdrew from treatment because of adverse events.[34]
- Azelnidipine monotherapy was also well tolerated during long-term administration (1 year), with 9 of 95 patients (9.5%) reporting adverse events such as mild headache, light-headedness and flushing.[33]
- Moreover, whereas mean heart rate in recipients of azelnidipine 16 mg/day decreased by 2 beats/min after 6 weeks of treatment (not statistically significant), heart rate had increased by 4 beats/min in amlodipine 5 mg/day recipients ($p < 0.001$ vs baseline and azelnidipine) in the randomised, double-blind study in 45 patients with mild-to-moderate hypertension (section 3).[15]
- In the pooled analysis,[36] of the 765 patients with hypertension who received azelnidipine for 12–52 weeks, 2.7% developed elevated serum levels of aspartate aminotransferase, alanine aminotransferase and/or bilirubin.

5. Dosage and Administration

The recommended starting dosage of azelnidipine is 8mg once daily administered orally after food, with titration to 16mg once daily as tolerated by the patient.[26] Caution should be used when administering the drug to the elderly and to patients with renal dysfunction (see section 2). Azelnidipine is contraindicated in pregnant women; concomitant administration with azole antifungal agents (e.g. itraconazole; see section 2) or with HIV protease inhibitors (e.g. ritonavir) is also contraindicated.[26]

6. Azelnidipine: Current Status

The use of azelnidipine in patients with hypertension has recently been approved in Japan. In clinical trials, azelnidipine effectively reduced blood pressure, showed efficacy similar to that of amlodipine or nitrendipine, and was generally well tolerated.

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