



CILNIDIPINE: A NOVEL APPROACH TO HYPERTENSION AND COMORBID CONDITIONS

Gulafsha Chaudhary

Department of Pharmacology,
School of pharmacy and
educational research (SPER)
Jamia Hamdard University,
Jamia Hamdard, Hamdard
University, Dr. Ambedkar
Nagar, Block D, Hamdard
Nagar, New Delhi, Delhi
110062

Khushi Sharma

Department of Pharmaceutics,
KIET school of pharmacy,
KIET group of institutions,
Ghaziabad-201206, Uttar
Pradesh, India

Dr. Prof. Ehtasamul Haque

Professor, Department of
Pharmacology, School of
Pharmaceutical Education, and
Research, Jamia Hamdard,
New Delhi

Corresponding author:

Gulafsha Chaudhary

Email:

Gulafshapharma2003@gmail.com

ABSTRACT

A prospective treatment for hypertension and related comorbidities, Cilnidipine is a fourth-generation dihydropyridine calcium channel blocker with a unique dual action on L-type and N-type calcium channels. Unlike traditional calcium channel blockers, it effectively lowers blood pressure without triggering reflex tachycardia. Additionally, its ability to inhibit excessive sympathetic activity provides significant organ-protective benefits, including reduced proteinuria, improved renal function, and enhanced insulin sensitivity. People with diabetes, metabolic syndrome, or chronic kidney disease will benefit most from this medication. Clinical research has shown that, in comparison to other calcium channel blockers like amlodipine, it is effective in reducing peripheral edema, lowering blood pressure, and improving tolerability. In addition to hypertension, cilnidipine has neuroprotective and stress-relieving properties and may be used to treat problems like congestive heart failure, neurological diseases, osteoporosis, and atherosclerosis. Its advantageous pharmacological profile, which includes better glucose management, enhanced lipid metabolism, and decreased oxidative stress, emphasizes how versatile it is as a therapeutic agent. Recent studies also point to its uses in cancer and pain treatment, highlighting its wide-ranging effectiveness. Although cilnidipine's dual-channel blocking makes it a better choice for long-term cardiovascular and systemic protection, more extensive research is required to completely determine its clinical usefulness in a range of patient types. Overall, this study suggested that cilnidipine stands out as a multifaceted therapeutic option with significant implications for long-term cardiovascular and systemic health.

Keywords: Cilnidipine, Hypertension management, Calcium channel blocker (CCB), L-type and N-type calcium channels, Reflex tachycardia, Sympathetic nervous system inhibition, Peripheral edema



Journal of Advanced Pharmaceutical Sciences and Natural Products

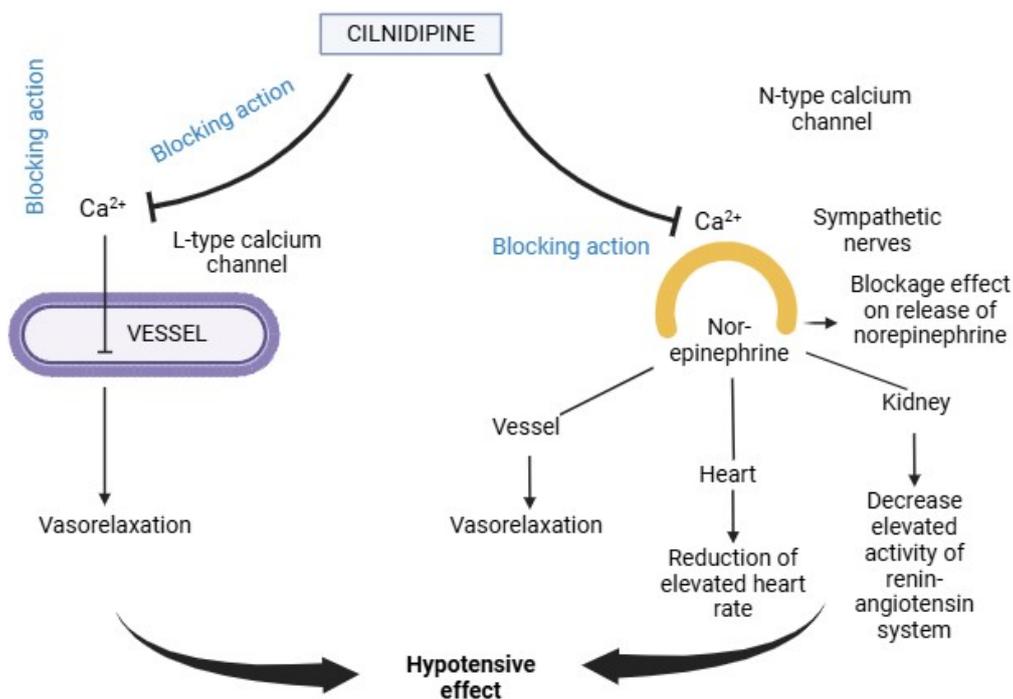
1. INTRODUCTION

A promising dual L/N type dihydropyridine calcium antagonist of the fourth generation is cilnidipine.¹ The powder form of cilnidipine is pale yellow. It dissolves somewhat in methanol and chloroform. C₂₇H₂₈N₂O₇ is its molecular formula. 1, 4-Dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridinedicarboxylic Acid 2-Methoxyethyl (2E)-3- Phenyl-2-propenyl Ester is the chemical name for cilnidipine. Cilnidipine has a molecular weight of 492.52.² Cilnidipine, an N-/L-type calcium channel blocker, inhibits structural, electrical, and autonomic remodeling linked to heart palpitations. The cardiovascular system is regulated neuro-hormonally when N-type calcium channels are blocked. This has positive benefits on preventing the advancement of renal disease, proteinuria, and other consequences of hypertension. A study on the tolerance of cilnidipine in hypertensive patients found that it is superior to amlodipine.^{3,4} Amlodipine and Cilnidipine are equally effective at lowering blood pressure in people with hypertension. However, as an N-type and L-type calcium channel blocker, cilnidipine is linked to a lower incidence of pedal oedema than amlodipine^{5,6} which only blocks L-type channels. Death, renal failure, myocardial infarction, and stroke can result from hypertension if not identified and given the proper care.⁷ It is the most prevalent ailment seen by primary care physicians. It is anticipated that by 2025, there will be close to 213 million of them.⁸ In India, 24% of fatalities from coronary heart disease and 57% of deaths from stroke are directly

attributable to hypertension.⁹ One of the first-line medications for the treatment of hypertension is CCB. Because it inhibits sympathetic N-type Ca²⁺ channels, Cilnidipine stands out among CCBs as a Ca²⁺ channel blocker. In addition to how it affects L-type Ca²⁺ channels by reducing the release of norepinephrine from sympathetic nerve endings, Cilnidipine causes vasodilatation, lowers heart rate, and increases blood flow to the kidneys. Compared to L-type CCB, cilnidipine has the advantage of producing less reflex tachycardia, less pedal oedema, and better control of proteinuria. By forcing the efferent arteriole to dilate, it reduces podocyte injury and glomeruli damage. Insulin sensitivity is also increased by cilnidipine. Cilnidipine is CCB, hence can be a suitable option for people with diabetes, hypertension, chronic renal disease, and other CCBs who are experiencing pedal oedema.¹⁰ The kidney is particularly vulnerable to high blood pressure. Therefore, a strict antihypertensive regimen is necessary for hypertensive individuals with renal problems, and cilnidipine has also been demonstrate renal protective properties in patients with renal impairment by reducing urine protein levels.¹¹

^{2.} Also according to recent studies, antagonists of N-type calcium channels may have neuroprotective effects and that these channels, not L-type ones, are crucial in neuronal cell death.¹²

2. Pharmacology of Cilnidipine



3. Clinical Applications or pharmacological properties against various diseases

a. Hypertension

Cilnidipine's antihypertensive effect has been shown in a number of research carried out in both in individuals with hypertension and those with severe hypertension. For one to three weeks, a once-daily dose of cilnidipine (5–20 mg) dramatically reduced the 24-hour average blood pressure from $149 \pm 4/88 \pm 2$ mmHg to $141 \pm 3/82 \pm 2$ mmHg while leaving the pulse rate unchanged. Thus, cilnidipine is a helpful

antihypertensive medication that would not result in reflex tachycardia or an extreme drop in blood pressure.¹³ Among patients

with mild to moderate essential hypertension, Minami J et al. did another study. Cilnidipine did not alter heart rate, however it did significantly lower 24-hour blood pressure by 6.5 ± 1.7 mm Hg systolic ($P < 0.01$) and 5.0 ± 1.1 mm Hg diastolic ($P < 0.01$). It was determined that cilnidipine has minimal effect on heart rate and is useful as a once-daily antihypertensive medication.¹⁴ A study by Kai T. et al. looked at how cilnidipine affected blood pressure, pulse rate, individuals who suffer from mild-to-moderate hypertension. Either the diastolic blood pressure dropped from 84 ± 11 mmHg to 71 ± 9 mmHg or the systolic blood pressure dropped from 151 ± 15 mmHg to 129 ± 14 mmHg. There were no notable variations in pulse rate noted.¹⁵



Journal of Advanced Pharmaceutical Sciences and Natural Products

b. Congestive Heart Failure

In experimental models of acute congestive heart failure, cilnidipine has demonstrated beneficial hemodynamic effects. Studies in canine models have shown that cilnidipine reduces aortic pressure and systemic vascular resistance while increasing aortic blood flow. Notably, unlike nicardipine, cilnidipine does not significantly elevate heart rate or cardiac contractility, suggesting a moderated reflex-induced sympathetic stimulation.¹⁶ Clinical studies on the long-term effects of cilnidipine in patients with chronic heart failure, particularly those with ischemic cardiomyopathy undergoing beta-blocker therapy, are limited. However, available research indicates that low-dose cilnidipine may be beneficial in such settings. Cilnidipine's inhibition of N-type calcium channels contributes to reduced cardiac sympathetic nerve activity. This effect is particularly advantageous in heart failure patients, as excessive sympathetic activation can exacerbate the condition. By attenuating this activity, cilnidipine may help in managing heart failure symptoms and progression. While traditional L-type calcium channel blockers like amlodipine are commonly used in hypertension management, their role in heart failure is more nuanced. Cilnidipine's dual blockade offers additional benefits by mitigating sympathetic overactivity, a factor that can adversely affect heart failure outcomes. This unique property may make cilnidipine a preferable option in certain heart failure populations. Cilnidipine's dual L/N-type calcium channel blocking properties confer

hemodynamic benefits and reduce sympathetic nerve activity, which may be advantageous in the management of congestive heart failure. While preclinical studies are promising, further clinical research is necessary to fully elucidate its therapeutic potential and establish comprehensive guidelines for its use in heart failure patients.^{27,18}

c. Renal

Numerous clinical investigations¹⁹ have revealed that cilnidipine exhibits superior renal protection when compared to with additional dihydropyridine CCBs and diuretics, among other antihypertensive medications.^{20,21} The specific processes by which cilnidipine produces its potent anti-proteinuric action are still unknown; nevertheless, podocyte protection may be a significant factor. Large molecules like albumin cannot flow through podocytes because they serve as a permeability barrier. The main sign of a compromised glomerular filtration barrier is an elevated level of albumin in the urine, which is referred to as "albuminuria" or "proteinuria." Numerous glomerular disorders that cause proteinuria also exhibit notable podocytes' structural damage. Proteinuria is now characterized by structural damage to podocytes, which also acts as a diagnostic indicator for a number of glomerular disorders.²² Moreover, diabetic nephropathy has been linked to a reduction in podocyte density and/or quantity.²³ Consequently, podocyte damage is seen as a key therapeutic target in hypertension patient renal illness.²⁴ Additionally, it was suggested that podocytes contain N-type



Journal of Advanced Pharmaceutical Sciences and Natural Products

calcium channels.²⁵ Cilnidipine shields glomeruli by efferent arteriolar vasodilation through the reduction of hypertension of the glomerulus. It is well established that this has a strong anti-proteinuric action by lowering glomerular pressure and providing efficient podocyte protection.²² Cilnidipine's favorable benefits in patients with metabolic syndrome may also be related to its inhibition of oxidative stress and renal RAS.²⁵ Several studies have investigated the antiproteinuric effects of amlodipine and cilnidipine. Kojima S. et al. analyzed their impact on proteinuria and renal function, finding that after 12 months of treatment, cilnidipine significantly reduced proteinuria, whereas amlodipine led to a notable increase.²⁵ Additionally, a randomized open-label study on CKD patients with an average eGFR of 6.0 examined cilnidipine's effects over a year. The results showed that patients receiving cilnidipine experienced a significant reduction in both proteinuria and heart rate, whereas those treated with an L-type calcium channel blocker saw an increase in proteinuria with no change in heart rate.²⁶

d. Neuro

Animal studies have demonstrated that cilnidipine can reduce neuronal damage.²⁷ It was found to maintain cerebral blood flow regardless of its effect on blood pressure, suggesting its potential suitability for hypertensive patients at risk of stroke.^{27,28} Furthermore, a clinical study using the cold pressor test indicated that cilnidipine reduced the risk of thrombosis associated with increased sympathetic activity, as evidenced by lower plasma

levels of β -thromboglobulin, a marker of platelet activation.²⁹ Cilnidipine has been shown to enhance cell viability in neuronally differentiated PC12 cells exposed to hydrogen peroxide-induced oxidative stress. This protective effect is attributed to its ability to scavenge free radicals and activate the phosphatidylinositol 3-kinase (PI3K) pathway. As a result, there is an increased expression of survival proteins like phosphorylated Akt and glycogen synthase kinase-3 β , along with a reduction in apoptotic markers such as cytosolic cytochrome c and activated caspase 3. Similarly, in primary cortical neuron cultures subjected to hypoxia, cilnidipine mitigates oxidative stress and limits calcium influx. It also regulates survival and death signaling proteins linked to the PI3K and extracellular signal-regulated kinase (ERK) pathways, thereby reducing apoptotic cell death. Moreover, cilnidipine inhibits microglial P2X7 receptors, which lowers the release of the proinflammatory cytokine IL-1 β , a key player in neuropathic pain. Collectively, these findings indicate that cilnidipine exerts neuroprotective effects through multiple mechanisms, including free radical scavenging, modulation of calcium influx, and activation of the PI3K and ERK pathways.⁵¹⁻⁵³

e. Insulin Sensitivity

Hypertensive patients who received cilnidipine at a daily dose of 5–10 mg for 12 weeks experienced a 20.8% increase in glucose infusion rate. This improvement in insulin sensitivity is likely due to cilnidipine's vasodilatory properties



Journal of Advanced Pharmaceutical Sciences and Natural Products

without triggering sympathetic nerve activation. Its positive impact on glucose metabolism is clinically relevant for managing hypertensive patients with insulin resistance or diabetes mellitus.³⁹ Additionally, hypertensive and obese patients treated with 10 mg of cilnidipine showed a reduction in insulin resistance.^{30,31}

f. Stress-relief and White coat hypertension

Stress is a well-recognized risk factor for cardiovascular diseases, including hypertension, playing a key role in both its onset and progression. Acute cold stress, a known trigger, elevates sympathetic activity by increasing plasma norepinephrine and epinephrine levels, leading to a rise in blood pressure without affecting heart rate. In spontaneously hypertensive rats, cilnidipine (3 mg/kg p.o.) significantly reduced the pressor response to acute cold stress compared to nifedipine, manidipine, or nifedipine. Although cilnidipine did not lower high baseline norepinephrine levels, it suppressed the acute cold stress-induced norepinephrine surge by approximately 25%, as well as the adrenaline increase associated with severe cold exposure.³²

In hypertensive patients, stress-induced sympathetic overactivity contributes to elevated blood pressure.³³ The phenomenon known as the **white coat (WC) effect** refers to a temporary rise in blood pressure observed in a clinical setting compared to ambulatory blood pressure monitoring.³⁴ This white coat hypertension is quantified by the difference between daytime

ambulatory blood pressure and in-clinic readings. Studies indicate that cilnidipine significantly reduces the white coat effect in individuals with essential hypertension.³³ Additionally, further research suggests that cilnidipine may be beneficial in managing both the white coat effect and morning hypertension, making it a potential antihypertensive option for morning blood pressure control.³⁵

g. Analgesic

Murakami et al. examined the antinociceptive properties of cilnidipine in mice, revealing its strong inhibition of N-type calcium channels.³⁶ By blocking these channels in the dorsal root ganglia, cilnidipine weakens synaptic neurotransmission, contributing to its pain-relieving effects.³⁶ Notably, unlike nifedipine, which failed to affect formalin-induced nociception in rats after oral administration, cilnidipine demonstrated superior analgesic efficacy compared to ziconotide while maintaining a better safety profile. Additionally, cilnidipine exerts its antinociceptive action at the spinal level, likely through the blockade of spinal N-type voltage-dependent calcium channels (VDCCs).³⁷

h. Atherosclerosis

In hypertensive patients, cilnidipine therapy has been associated with an improved lipid profile, notably a reduction in total cholesterol, although its impact on fibrinolytic markers has been inconsistent. The metabolic connection between fibrinolysis and favorable lipid modifications could provide deeper insights



Journal of Advanced Pharmaceutical Sciences and Natural Products

into the antiatherogenic effects of cilnidipine in hypertension management.³⁸ Studies in hypertensive rats suggest that cilnidipine exhibits a superior lipid-lowering effect compared to diltiazem and amlodipine.³⁹ Research by Tan et al. indicates that cilnidipine may contribute to balancing fibrinolytic activity in hypertensive patients.⁴⁰ After three months of treatment, individuals with moderate baseline levels of lipoproteins, serum lipids, and fibrinolytic parameters (total lipid profile ranging from 240 to 300 mg/dL) showed no significant changes. However, findings by Ahaneku et al. suggest that hypertensive patients with initially high total cholesterol levels (>300 mg/dL) experienced an increase in high-density lipoprotein (HDL) cholesterol and a reduction in total cholesterol.⁴¹

I. Osteoporosis

Cilnidipine, a dual L-/N-type calcium channel blocker, has shown potential in protecting against osteoporosis in experimental studies. Research conducted on ovariectomized hypertensive rats revealed that cilnidipine treatment led to a significant rise in the ratio of alkaline phosphatase to tartrate-resistant acid phosphatase, suggesting improved bone formation. Moreover, the number of osteoclasts decreased notably, and bone mineral density increased significantly compared to the control group. These effects are believed to result from cilnidipine's inhibition of N-type calcium channels, which helps suppress sympathetic nervous activity and, in turn, reduces bone resorption. These findings indicate that cilnidipine may offer

therapeutic benefits beyond its role in blood pressure management, particularly as a potential treatment for osteoporosis in hypertensive postmenopausal women. However, further clinical studies are required to validate these effects in human populations.⁵⁴ Antihypertensive drugs like carvedilol and cilnidipine may be beneficial for hypertensive postmenopausal women, as osteoporosis is a leading cause of bone fractures in both the elderly and postmenopausal populations.⁴²

j. Cancer

Studies suggest that cilnidipine exhibits cytotoxic effects on cancer cells by inducing oxidative damage, similar to the mechanism of action observed in conventional anticancer drugs. Moreover, by inhibiting N-type calcium channels, cilnidipine may help reduce sympathetic nervous system activity, which plays a role in cancer progression. Additionally, certain antihypertensive drugs, including calcium channel blockers like cilnidipine, have been linked to increased intracellular calcium accumulation, ultimately triggering apoptosis in cancer cells. These findings indicate that cilnidipine could be a promising adjunctive therapy in cancer treatment. However, further clinical research is essential to validate its efficacy and safety in this context.^{55,56}

A study using human aortic smooth muscle cells, lung carcinoma cell line (A549 cells), and human umbilical vein endothelial cells showed that cilnidipine significantly lowers hypoxia-induced factor-1 (HIF-1) activity



Journal of Advanced Pharmaceutical Sciences and Natural Products

and downstream gene expressions in a cell type-specific way.⁴³

5. Comparison of Cilnidipine with other Calcium channel blockers

Cilnidipine, a fourth-generation calcium channel blocker (CCB), distinguishes itself from other CCBs like amlodipine, nifedipine, and diltiazem due to its dual inhibition of both L-type and N-type calcium channels. While L-type calcium channel blockade, a shared mechanism among all CCBs, promotes vascular smooth muscle relaxation and lowers blood pressure by reducing vascular resistance, cilnidipine's additional inhibition of N-type calcium channels on sympathetic nerve terminals decreases norepinephrine release, thereby suppressing sympathetic nervous system activity. This dual action enables cilnidipine to effectively reduce blood pressure without inducing reflex tachycardia, a common limitation of other CCBs like amlodipine.⁴⁴ Reflex tachycardia, which arises as a compensatory response to vasodilation, can increase cardiac workload, making cilnidipine's ability to prevent this response particularly advantageous for patients with cardiovascular risks.

Regarding its side effect profile, cilnidipine has been associated with a significantly lower incidence of peripheral edema compared to other dihydropyridine CCBs such as amlodipine. Peripheral edema, a frequent adverse effect of many CCBs, results from increased capillary hydrostatic pressure due to selective arterial vasodilation. Cilnidipine's ability to reduce sympathetic outflow likely mitigates this

effect, enhancing its tolerability and improving patient adherence to treatment.⁴⁵ Beyond blood pressure control, cilnidipine has demonstrated notable organ-protective properties, especially in hypertensive patients with comorbidities like chronic kidney disease (CKD) and diabetes. By inhibiting N-type calcium channels, it reduces proteinuria and slows the progression of renal damage, a benefit not typically observed with L-type selective CCBs like amlodipine.⁴⁶ Additionally, cilnidipine has shown promise in preventing cardiac remodeling and improving diastolic function. Research suggests that when combined with renin-angiotensin system inhibitors such as valsartan, cilnidipine provides greater protection against cardiac remodeling compared to amlodipine in similar treatment regimens.⁴⁷ These findings highlight its potential in managing hypertension in patients with elevated cardiovascular risks.

Moreover, cilnidipine's ability to modulate sympathetic activity may offer neuroprotective benefits, making it a valuable treatment option for hypertensive patients at risk of stroke or those with existing cerebrovascular conditions. While CCBs like amlodipine remain widely used for their efficacy in lowering blood pressure, cilnidipine's dual mechanism provides distinct advantages, including reduced reflex tachycardia, lower peripheral edema incidence, and significant organ-protective effects.

These characteristics make cilnidipine a compelling choice for hypertensive patients with coexisting conditions such as CKD,



Journal of Advanced Pharmaceutical Sciences and Natural Products

diabetes, or heart failure, where effective blood pressure control and systemic protection are crucial. With its extensive therapeutic benefits and favorable safety profile, cilnidipine emerges as a promising option for long-term cardiovascular and renal health in diverse patient populations.

6. Tolerability and Safety Profile of Cilnidipine/ Adverse Effects

The combination of valsartan and cilnidipine is well tolerated without showing any pharmacokinetic and pharmacodynamics interactions or adverse effects.⁴⁸ Cilnidipine and amlodipine are both equipotent drugs with the same dose amount, but cilnidipine has better safety and tolerability profile than amlodipine.⁴⁹ The combination of chlorthalidone and cilnidipine significantly reduced blood pressure and is well tolerated compared to amlodipine and hydrochlorothiazide.⁵⁰ Cilnidipine, a fourth-generation calcium channel blocker, is generally well-tolerated, but like any medication, it is associated with certain adverse effects. While it is known for causing significantly less

peripheral edema compared to other dihydropyridine calcium channel blockers (CCBs) due to its N-type calcium channel inhibition, this side effect can still occur in some patients. Commonly reported adverse effects include dizziness and headache, which are typical of vasodilatory drugs and generally mild and transient. Orthostatic hypotension may also occur, particularly in elderly patients, as a result of excessive vasodilation or reduced sympathetic activity from N-type channel blockade. Fatigue and weakness have been noted and are attributed to reduced blood pressure and sympathetic tone. Rarely, cilnidipine can cause bradycardia due to its inhibition of sympathetic outflow, and hypersensitivity reactions such as skin rash or pruritus have been reported in isolated cases. Gastrointestinal symptoms like nausea are infrequent but possible. While these adverse effects are usually mild, clinicians should exercise caution when prescribing cilnidipine to elderly or polypharmacy patients and monitor for potential side effects, ensuring its benefits outweigh the risks.^{44,45}

Table 1; Comprehensive Summary of Cilnidipine's Therapeutic Effects

Condition	Mechanism of Action	Key Study Findings	Clinical Implications
Hypertension	Blocks L/N-type calcium channels, leading to vasodilation without reflex tachycardia.	SBP reduced from 149±4 mmHg to 141±3 mmHg, DBP from 88±2 mmHg to 82±2 mmHg. No change in heart rate. [13]	Effective for mild-to-moderate hypertension; safer than other CCBs for patients at risk of tachycardia.
Congestive Heart Failure (CHF)	Lowers aortic pressure and systemic vascular resistance while preventing excessive sympathetic activation.	In canine models, reduced aortic pressure and increased blood flow without raising heart rate. [16]	May benefit CHF patients with high sympathetic tone and ischemic cardiomyopathy.
Renal Protection	Efferent arteriolar vasodilation reduces glomerular hypertension, leading to lower proteinuria.	Cilnidipine reduced proteinuria significantly compared to amlodipine. [25,26]	Preferred antihypertensive for CKD patients due to its anti-proteinuric effect.



Journal of Advanced Pharmaceutical Sciences and Natural Products

Neuroprotection	Maintains cerebral blood flow and reduces neuronal damage.	Prevents stroke risks by maintaining blood flow, independent of BP changes. [27]	Useful for hypertensive patients at risk of stroke.
Insulin Sensitivity	Reduces sympathetic nerve activation, leading to enhanced insulin sensitivity.	20.8% increase in glucose infusion rate in hypertensive diabetic patients. [30,31]	Suitable for hypertensive patients with insulin resistance or diabetes.
Stress & White Coat Hypertension	Reduces sympathetic overactivity and suppresses norepinephrine spikes caused by stress.	Suppressed norepinephrine response by 25%, reducing white coat hypertension. [32,33]	Effective for stress-related BP elevations and morning hypertension.
Analgesic Effect	Blocks N-type calcium channels in spinal cord and dorsal root ganglia, reducing pain perception.	More effective than ziconotide for pain relief; superior to nifedipine in formalin-induced pain model. [36]	Potential use in neuropathic pain management.
Atherosclerosis	Improves lipid profile, reduces oxidative stress, and enhances fibrinolytic balance.	Increased HDL, reduced total cholesterol in patients with baseline >300 mg/dL. [40,41]	Cardio-protective effect in hypertensive patients with dyslipidemia.
Osteoporosis	Regulates calcium metabolism and reduces bone loss in hypertensive conditions.	Reduced osteoporosis in hypertensive ovariectomized rats. [42]	May benefit postmenopausal women with hypertension and osteoporosis.
Cancer	Inhibits hypoxia-induced factor-1 (HIF-1), reducing tumor growth signaling.	Reduced HIF-1 activity in lung carcinoma cells (A549). [43]	Potential role in cancer therapy, but requires further clinical research.

5. Formulation of Cilnidipine available in Pharmaceutical market⁴³

Brand Name	Manufacturer	Country	Dosage form (mg)
Atelec	Ajinomoto Pharmaceutical	Japan, Vietnam	Not specified
Cilacar	Not specified	India	5,10,20
Cilaheart	Not specified	India	5,10,20
Cinod	Not specified	India	5,10,20
Nexovas	Macleods	India	Not specified
Nexovas-CH	Macleods	India	Not specified
Nexocas-O	Macleods	India	Not specified
Atedio	EA Pharma	Japan	Not specified
Cilnidipine	Daiko Seiyaku, Nihon Generic, Sawai Seiyaku, Shiono Kemikaru, Takeda Teva Pharma	Japan	Not specified
Cilnidipine-Xinya	New Asiatic Pharm	China	Not specified
Jiuyue	Jiu Dian Pharmaceutical	China	Not specified
CCAD	Not specified	India	5,10,20
CD Pin	Not specified	India	5,10
Cilacar-C	J.B. Chemicals & Pharmaceuticals	India	10/6.25, 10/12.5



Journal of Advanced Pharmaceutical Sciences and Natural Products

Cilacar-M	J.B. Chemicals & Pharmaceuticals	India	10/50
Cilacar-T	J.B. Chemicals & Pharmaceuticals	India	10/40, 10/80
Cilacar-TC	J.B. Chemicals & Pharmaceuticals	India	10/40/6.25, 10/40/12.5
Cilagard	Not specified	India	5,10
Trinexovas	Macleods Pharmaceuticals	India	10/20/12.5, 10/40/12.5

7. Future Perspective of Cilnidipine

Cilnidipine, a new-generation dihydropyridine calcium channel blocker (CCB), has garnered significant attention due to its unique ability to block both L-type and N-type calcium channels, setting it apart from conventional CCBs like amlodipine. This distinctive pharmacological action enables cilnidipine to effectively lower blood pressure while minimizing adverse effects such as reflex tachycardia and excessive sympathetic activation. With its superior hemodynamic benefits and potential organ-protective properties, cilnidipine is increasingly recognized as a promising antihypertensive agent with broad therapeutic applications. A key area where cilnidipine shows great promise is in managing complications associated with hypertension, particularly in patients with chronic kidney disease (CKD) and diabetes mellitus. Research has highlighted its renoprotective effects, as it helps reduce proteinuria and glomerular hypertension, making it a valuable choice for hypertensive individuals with kidney impairment.⁵⁷ Additionally, its ability to suppress sympathetic nervous system activity may contribute to improved glycemic control in diabetic patients, thereby lowering the risk of cardiovascular events. Another potential application of cilnidipine is in the management of heart failure. Unlike traditional CCBs, which can

aggravate heart failure by triggering reflex sympathetic activation, cilnidipine's ability to block N-type calcium channels helps reduce sympathetic nerve activity, leading to improved cardiac function and a lower risk of arrhythmias.⁵⁸ This makes cilnidipine a compelling option for hypertensive patients with concurrent heart failure or those at risk of developing cardiovascular complications. Furthermore, emerging research suggests that cilnidipine offers additional benefits beyond blood pressure control. Studies indicate its potential role in enhancing endothelial function, reducing arterial stiffness, and exerting anti-inflammatory effects, all of which are essential in preventing atherosclerosis and related cardiovascular diseases.⁵⁹ These multifaceted benefits position cilnidipine as a favorable first-line antihypertensive therapy, particularly for elderly patients and those with metabolic syndrome. The drug's excellent safety profile further strengthens its future role in clinical practice. Compared to conventional CCBs, cilnidipine is associated with a significantly lower incidence of pedal edema, a common side effect that often leads to treatment discontinuation.⁶⁰ This improved tolerability can enhance patient adherence and long-term treatment outcomes, making cilnidipine a preferred choice for hypertension management.



Journal of Advanced Pharmaceutical Sciences and Natural Products

In summary, cilnidipine's future looks highly promising, with expanding clinical indications and growing evidence supporting its efficacy and safety across diverse patient populations. Its dual-channel blockade provides distinct advantages over traditional CCBs, particularly in preserving target organ function, reducing sympathetic overactivation, and improving overall cardiovascular health. Further clinical trials and real-world studies will continue to refine its role in hypertension management and explore its potential in other cardiovascular and metabolic conditions.

8. Conclusion

Cilnidipine, a fourth-generation calcium channel blocker, demonstrates remarkable potential for advancing hypertension management and related comorbidities due to its dual action on L-type and N-type calcium channels. Unlike traditional calcium channel blockers, cilnidipine not only promotes vasodilation by inhibiting L-type calcium channels but also suppresses sympathetic overactivity through N-type calcium channel blockade. This dual mechanism uniquely addresses reflex tachycardia and reduces peripheral edema, commonly seen with other dihydropyridine calcium channel blockers. Cilnidipine's ability to lower blood pressure effectively without adversely impacting heart rate positions it as a superior antihypertensive option, particularly for patients with cardiovascular risks. Additionally, its organ-protective properties, including renoprotection and potential benefits in mitigating proteinuria and podocyte injury,

make it a compelling choice for patients with chronic kidney disease or diabetes. Emerging evidence also suggests that cilnidipine may confer neuroprotective effects, reduce oxidative stress, improve insulin sensitivity, and provide therapeutic benefits for stress-related hypertension and morning surges in blood pressure. Moreover, its tolerability and favorable side effect profile, including reduced peripheral edema and improved metabolic outcomes, enhance patient compliance and treatment satisfaction. While preclinical studies and early clinical trials highlight cilnidipine's potential in addressing conditions such as congestive heart failure, neurodegenerative disorders, and even osteoporosis, further large-scale, multicenter trials are essential to establish comprehensive clinical guidelines and expand its therapeutic applications. Overall, cilnidipine represents a significant advancement in calcium channel blocker therapy, offering a multifaceted approach to hypertension management and related systemic complications.

REFERENCES

1. Kumar S. Hypertension management: Old drug revisited-Cilnidipine. *Journal of Clinical and Preventive Cardiology*. 2017 Jan 1;6(1):24-6.



Journal of Advanced Pharmaceutical Sciences and Natural Products

2. Chatki PK, Tabassum S. Analytical Methods of Dihydropyridines Based Calcium Channel Blockers- Amlodipine, Lacidipine, Isradipine, Nifedipine, Felodipine, Cilnidipine and its related formulations: A Review.
3. Tajiri K, Guichard JB, Qi X, Xiong F, Naud P, Tardif JC, Costa AD, Aonuma K, Nattel S. An N-/L-type calcium channel blocker, cilnidipine, suppresses autonomic, electrical, and structural remodelling associated with atrial fibrillation. *Cardiovascular Research*. 2019 Dec 1;115(14):1975-85.
4. Dharpur P, Kavitha VC. A study at BRIMS hospital for comparing the tolerability of cilnidipine and amlodipine in the treatment of hypertension. *Indian J Pharm Pharmacol*. 2019;6(1):11-3.
5. Adake P, Somashekar HS, Rafeeq PM, Umar D, Basheer B, Baroudi K. Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. *Journal of advanced pharmaceutical technology & research*. 2015 Apr 1;6(2):81-5.
6. Gopinath S, Harishkumar VV, Santhosh VC, Puthalath S. Case report on low dose of Cilnidipine: A fourth-generation calcium channel blocker-induced gingival overgrowth. *Journal of Indian Society of Periodontology*. 2019 Jul 1;23(4):377-80.
7. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama*. 2014 Feb 5;311(5):507-20.
8. Mohan S, Campbell N, Chockalingam A. Time to effectively address hypertension in India. *Indian Journal of Medical Research*. 2013 Apr 1;137(4):627-31.
9. Gupta R. Trends in hypertension epidemiology in India. *Journal of human hypertension*. 2004 Feb;18(2):73-8.
10. Shete MM. Cilnidipine: next generation calcium channel blocker. *J Assoc Physicians India*. 2016 Apr 1;64(4):95-9.
11. Morimoto S, Yano Y, Maki K, Iwasaka T. Renal and vascular protective effects of cilnidipine in patients with essential hypertension. *Journal of hypertension*. 2007 Oct 1;25(10):2178-83.
12. Lee YJ, Park KH, Park HH, Kim YJ, Lee KY, Kim SH, Koh SH. Cilnidipine mediates a neuroprotective effect by scavenging free radicals and activating the phosphatidylinositol 3-kinase pathway. *Journal of neurochemistry*. 2009 Oct;111(1):90-100.
13. Tominaga M, Ohya Y, Tsukashima A, Kobayashi K, Takata Y, Koga T, Yamashita Y, Fujishima Y, Abe I, Fujishima M. Ambulatory blood pressure monitoring in patients with essential hypertension treated with a new calcium antagonist, cilnidipine. *Cardiovascular drugs and therapy*. 1997 Mar;11:43-8.



Journal of Advanced Pharmaceutical Sciences and Natural Products

14. Minami J, Kawano Y, Makino Y, Matsuoka H, Takishita S. Effects of cilnidipine, a novel dihydropyridine calcium antagonist, on autonomic function, ambulatory blood pressure and heart rate in patients with essential hypertension. *British journal of clinical pharmacology*. 2000 Dec;50(6):615-20.
15. Kai T, Kuzumoto Y. Effects of a dual L/N-type calcium channel blocker cilnidipine on blood pressure, pulse rate, and autonomic functions in patients with mild to moderate hypertension. *Clinical and Experimental Hypertension*. 2009 Nov 1;31(7):595-604.
16. Noguchi K, Matsuzaki T, Koyama T, Itomine T, Sakanashi M. Comparison of haemodynamic responses to cilnidipine and nicardipine in an experimental model of acute congestive heart failure. *Clinical and experimental pharmacology and physiology*. 1998 Aug;25(7-8):541-7.
17. Kitada H, Noda Y, Sasaki T, Miyatake K. Long-term effects of low-dose cilnidipine in patients with chronic heart failure due to ischemic cardiomyopathy during beta-blocker therapy. *Journal of Cardiac Failure*. 2008;7(14):S152.
18. Sakata K, Shirohara M, Yoshida H, Nawada R, Obayashi K, Togi K, Miho N. Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *Hypertension*. 1999 Jun;33(6):1447-52.
19. Rose GW, Kanno Y, Ikebukuro H, Kaneko M, Kaneko K, Kanno T, Ishida Y, Suzuki H. Cilnidipine is as effective as benazepril for control of blood pressure and proteinuria in hypertensive patients with benign nephrosclerosis. *Hypertension Research*. 2001;24(4):377-83.
20. Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, Takahashi K. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. *Kidney international*. 2007 Dec 2;72(12):1543-9.
21. Arif E, Nihalani D. Podocytes as a therapeutic target. *Ann Clin Exp Hypertension*. 2013;1(1):1004.
22. Giunti S, Barit D, Cooper ME. Mechanisms of diabetic nephropathy: role of hypertension. *Hypertension*. 2006 Oct 1;48(4):519-26.
23. Giunti S, Barit D, Cooper ME. Mechanisms of diabetic nephropathy: role of hypertension. *Hypertension*. 2006 Oct 1;48(4):519-26.
24. Fan YY, Kohno M, Nakano D, Ohsaki H, Kobori H, Suwarni D, Ohashi N, Hitomi H, Asanuma K, Noma T, Tomino Y. Cilnidipine suppresses podocyte injury and proteinuria in metabolic syndrome rats: possible involvement of N-type calcium channel in podocyte. *Journal of hypertension*. 2010 May 1;28(5):1034-43.
25. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertension Research*. 2004;27(6):379-85.



Journal of Advanced Pharmaceutical Sciences and Natural Products

26. Hatta T, Takeda K, Shiotsu Y, Sugishita C, Adachi T, Kimura T, Sonomura K, Kusaba T, Kishimoto N, Narumiya H, Tanda S. Switching to an L/N-type calcium channel blocker shows renoprotective effects in patients with chronic kidney disease: the Kyoto Cilnidipine Study. *Journal of International Medical Research*. 2012 Aug;40(4):1417-28.
27. Takahara A, Konda T, Enomoto A, Kondo N. Neuroprotective effects of a dual L/N-type Ca²⁺ channel blocker cilnidipine in the rat focal brain ischemia model. *Biological and Pharmaceutical Bulletin*. 2004;27(9):1388-91.
28. Watanabe K, Dozen M, Hayashi Y. Effect of cilnidipine (FRC-8653) on autoregulation of cerebral blood flow. *Nihon Yakurigaku zasshi. Folia Pharmacologica Japonica*. 1995 Dec 1;106(6):393-9.
29. Tomiyama H, Kimura Y, Kuwabara Y, Maruyama C, Yoshida Y, Kuwata S, Kinouchi T, Yoshida H, Doba N. Cilnidipine more highly attenuates cold pressor stress-induced platelet activation in hypertension than does amlodipine. *Hypertension Research*. 2001;24(6):679-84
30. Yagi S, Goto S, Yamamoto T, Kurihara S, Katayama S. Effect of cilnidipine on insulin sensitivity in patients with essential hypertension. *Hypertension Research*. 2003;26(5):383-7.
31. Ueshiba H, Miyachi Y. Effects of the long-acting calcium channel blockers, amlodipine, manidipine and cilnidipine on steroid hormones and insulin resistance in hypertensive obese patients. *Internal medicine*. 2004;43(7):561-5.
32. Hosono M, Hiruma T, Watanabe K, Hayashi Y, Ohnishi H, Takata Y, Kato H. Inhibitory effect of cilnidipine on pressor response to acute cold stress in spontaneously hypertensive rats. *The Japanese Journal of Pharmacology*. 1995;69(2):119-25.
33. Morimoto, S.; Takeda, K.; Oguni, A.; Kido, H.; Harada, S.; Moriguchi, J.; Itoh, H.; Nakata, T.; Sasaki, S.; Nakagawa, M. Reduction of white coat effect by cilnidipine in essential hypertension. *Am. J. Hypertens.*, 2001, 14(10), 1053-1057.
34. Matsuoka S, Kawamura K, Honda M, Awazu M. White coat effect and white coat hypertension in pediatric patients. *Pediatric Nephrology*. 2002 Nov;17:950-3.
35. Yamagishi T. Beneficial effect of cilnidipine on morning hypertension and white-coat effect in patients with essential hypertension. *Hypertension research*. 2006 May;29(5):339-44
36. Murakami M, Nakagawasai O, Fujii S, Hosono M, Hozumi S, Esashi A, Taniguchi R, Okamura T, Suzuki T, Sasano H, Yanagisawa T. Antinociceptive effect of cilnidipine, a novel N-type calcium channel antagonist. *Brain research*. 2000 Jun 16;868(1):123-7.
37. Koganei H, Shoji M, Iwata S. Suppression of formalin-induced nociception by cilnidipine, a voltage-dependent calcium channel blocker.



Journal of Advanced Pharmaceutical Sciences and Natural Products

- Biological and Pharmaceutical Bulletin. 2009 Oct 1;32(10):1695-700
38. Ahaneku JE, Sakata K, Uranol T, Takada Y, Takada A. Effects of cilnidipine on lipids, lipoproteins and fibrinolytic system in hypertensive patients. *Drugs under experimental and clinical research*. 2000 Jan 1;26(4):119-23.
 39. Dangi, N.B.; Sudheer, A.; Rathod, S.P.; Sapkota, H.P. Effect of Amlodipine, Cilnidipine and Diltiazem on lipid profiles of hypertensive rats fed with high fat diet: A comparative study. *Bull. Fac. Pharm. Cairo Univ.*, 2016, 54(2), 137-143.
 40. Tan HW, Li L, Zhang W, Ma ZY, Zhong XZ, Li JJ, Wang Y. Effects of cilnidipine on fibrinolysis in Chinese hypertensive patients. *Clinical drug investigation*. 2005 Dec;25:777-83.
 41. Ahaneku JE, Sakata K, Urano T, Takada Y, Takada A. Influence of baseline values on lipids, lipoproteins and fibrinolytic parameters during treatment of hypertension with cilnidipine. *Pharmacological research*. 2000 Jan 1;41(1):79-82.
 42. Shimizu H, Nakagami H, Yasumasa N, Mariana OK, Kyutoku M, Koriyama H, Nakagami F, Shimamura M, Rakugi H, Morishita R. Cilnidipine, but not amlodipine, ameliorates osteoporosis in ovariectomized hypertensive rats through inhibition of the N-type calcium channel. *Hypertension Research*. 2012 Jan;35(1):77-81.
 43. Oda S, Oda T, Takabuchi S, Nishi K, Wakamatsu T, Tanaka T, Adachi T, Fukuda K, Nohara R, Hirota K. The calcium channel blocker cilnidipine selectively suppresses hypoxia-inducible factor 1 activity in vascular cells. *European journal of pharmacology*. 2009 Mar 15;606(1-3):130-6.
 44. Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K. Comparison of the effects of cilnidipine and amlodipine on ambulatory blood pressure. *Hypertension research*. 2005 Dec;28(12):1003-8.
 45. Wang AL, Iadecola C, Wang G. New generations of dihydropyridines for treatment of hypertension. *Journal of geriatric cardiology: JGC*. 2017 Jan;14(1):67.
 46. Chandra KS, Ramesh G. The fourth-generation Calcium channel blocker: Cilnidipine. *Indian heart journal*. 2013 Dec 1;65(6):691-5.
 47. Nagasawa K, Takahashi K, Matsuura N, Takatsu M, Hattori T, Watanabe S, Harada E, Niinuma K, Murohara T, Nagata K. Comparative effects of valsartan in combination with cilnidipine or amlodipine on cardiac remodeling and diastolic dysfunction in Dahl salt-sensitive rats. *Hypertension Research*. 2015 Jan;38(1):39-47.
 48. Lee J, Lee H, Jang K, Lim KS, Shin D, Yu KS. Evaluation of the pharmacokinetic and pharmacodynamic drug interactions between cilnidipine and valsartan, in healthy volunteers. *Drug design, development and therapy*. 2014 Oct 8:1781-8.
 49. Mohanty, M.; Tripathy, K.P.; Srakar, S.; Srivastava, V. Evaluation of safety



Journal of Advanced Pharmaceutical Sciences and Natural Products

- and tolerability of amlodipine and cilnidipine-A comparative study. *Sch. J. App. Med. Sci*, 2016, 4(8C), 2884-28.
50. Sagarad SV, HP S. A prospective and open label study of use of cilnidipine and chlorthalidone fixed dose combination in Indian hypertensive patients, intolerant or uncontrolled on amlodipine and hydrochlorothiazide combination. *International Journal of Advances in Medicine*. 2017 Nov;4(6):1522.
 51. Lee YJ, Park KH, Park HH, Kim YJ, Lee KY, Kim SH, Koh SH. Cilnidipine mediates a neuroprotective effect by scavenging free radicals and activating the phosphatidylinositol 3-kinase pathway. *Journal of neurochemistry*. 2009 Oct;111(1):90-100.
 52. Kim S, Lee KY, Koh SH, Park HH, Yu HJ, Lee YJ. Role of the phosphatidylinositol 3-kinase and extracellular signal-regulated kinase pathways in the neuroprotective effects of cilnidipine against hypoxia in a primary culture of cortical neurons. *Neurochemistry international*. 2012 Dec 1;61(7):1172-82.
 53. Yamashita T, Kamikaseda S, Tanaka A, Tozaki-Saitoh H, Caaveiro JM, Inoue K, Tsuda M. New inhibitory effects of cilnidipine on microglial P2X7 receptors and IL-1 β release: an involvement in its alleviating effect on neuropathic pain. *Cells*. 2021 Feb 18;10(2):434.
 54. Shimizu H, Nakagami H, Yasumasa N, Mariana OK, Kyutoku M, Koriyama H, Nakagami F, Shimamura M, Rakugi H, Morishita R. Cilnidipine, but not amlodipine, ameliorates osteoporosis in ovariectomized hypertensive rats through inhibition of the N-type calcium channel. *Hypertension Research*. 2012 Jan;35(1):77-81.
 55. PR P, Mohapatra S, Rani JR, James J. Negative Effect on the Anti-Oxidant Potential of Cilnidipine in Breast Cancer Cell Lines-An in Vitro Study. *Journal of Pharmaceutical Negative Results*. 2022 Oct 7;13.
 56. Takahara A. Cilnidipine: a new generation Ca²⁺ channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovascular therapeutics*. 2009 Jun;27(2):124-39.
 57. Uchida S, Takahashi M, Sugawara M, Saito T, Nakai K, Fujita M, Mochizuki K, Shin I, Morita T, Hikita T, Itakura H. Effects of the N/L-Type Calcium Channel Blocker Cilnidipine on Nephropathy and Uric Acid Metabolism in Hypertensive Patients With Chronic Kidney Disease (J-CIRCLE Study). *The Journal of Clinical Hypertension*. 2014 Oct;16(10):746-53.
 58. Konda, T., Inoue, T., Mizushima, T., Tagawa, M., & Koshiyama, H. (2017). Sympathetic inhibition by cilnidipine contributes to blood pressure reduction and renoprotection in hypertensive patients with diabetes. *Hypertension Research*, 40(7), 644-649.
 59. Takahashi, A., Nishikawa, H., Fukuda, K., et al. (2014). Cilnidipine improves endothelial function and arterial stiffness in hypertensive patients.



Journal of Advanced Pharmaceutical Sciences and Natural Products

Journal of Hypertension, 32(2), 405-412.

60. Matsui, Y., Eguchi, K., Orita, Y., et al. (2012). Comparison of cilnidipine and amlodipine in preventing pedal edema in hypertensive patients. *Hypertension Research*, 35(10), 1057-1061.