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Improved Formulation of Cilnidipine versus Conventional Cilnidipine in Treatment of Essential Hypertension: A Double-Blind, Randomized, Comparative Study

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***Abstract*: *Background*: Cilnidipine, a calcium channel blocker, has a two-directional approach in hypertension management. *Methods:* We conducted a randomized, double-blind, parallel-group study to evaluate and compare the efficacy and safety of improved formulation of cilnidipine 10 mg tablet (Nexovas®, Macleods, India), which was bioequivalent to the Atelec® (Japan) ,versus conventional cilnidipine (India) in patients with essential hypertension. Patients were randomized 1:1 to Nexovas® or conventional cilnidipine groups. The treatment was administered for 30 days. *Results:* Overall, the mean change from baseline to day 30 in systolic blood pressure (SBP) was found to be 21 and 16 mmHg and in diastolic BP (DBP) was found to be 11 and 9 mmHg with improved formulation of cilnidipine 10 mg tablet (Nexovas®) and conventional cilnidipine, respectively, which was statistically significant. In addition, there was a higher mean improvement in BP on day 15 and higher reduction in spot urine-protein creatinine ratio (Day 30) in patients treated with Nexovas®. The goal BP (<140/90) was achieved in higher percentage of patients taking Nexovas® versus conventional cilnidipine (SBP 93.33% vs. 80.00%; DBP 80.00% vs. 53.33%. *Conclusion*: The improved formulation of cilnidipine 10 mg (Nexovas®) demonstrated super dissolution when compared to the conventional cilnidipine, was bioequivalent to Atelec®, and in clinical efficacy and safety trial showed statistically significant improvement in BP after one month of treatment. Goal BP (<140/90 mmHg) was achieved in higher proportion of patients treated with the Nexovas® compared to the conventional cilnidipine in India.**

***Keywords*: Blood pressure, Calcium channel blocker, Cilnidipine, Diastolic, Hypertension, and Systolic.**

1. Introduction

Hypertension, a leading cause of morbidity and mortality, is a major public health concern in India. Even slightest reductions in elevated blood pressure (BP) can be effective in managing the BP-related complications associated with cardiovascular system and leading to end-organ damage. As per the 8th Joint National Committee (JNC), the goal BP in adults younger than 60 years of age should be <140/90 mmHg, and treatment can be initiated from any one of the following classes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers (CCBs), or diuretics [1-3]. CCBs are the commonly used first-line antihypertensive agents. This class of compound inhibits voltage-gated calcium channels in the myocardium and vasculature and reduces muscle contractility in these tissues and decreases cardiac output along with total peripheral resistance [1, 3].

Cilnidipine, a CCB, blocks the incoming calcium and suppresses the concentration of blood vessels. It acts on the L-type calcium channels of the blood vessels, which are long-opening high-voltage-gated calcium channel. Thus, it effectively reduces BP by blocking the entry of calcium and stopping the contraction of blood vessels. In addition, it shows activity on the N-type calcium channel in the end of the sympathetic nerve inhibiting the emission of norepinephrine and suppressing the increase in stress BP. This dual or two-directional approach for reducing the elevated BP in patients with hypertension is the uniqueness of cilnidipine [1]. Various studies demonstrate the antihypertensive effect of cilnidipine and its superiority over amlodipine. Literature regarding clinical experience of cilnidipine suggests that it has renoprotective and vasoprotective properties, and it also demonstrate improvement in the left-ventricular midwall function independent of BP changes in hypertension [4,5]. As

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per available published literature, administration of cilnidipine improves left-ventricular systolic and diastolic function and decreased left ventricular mass in essential hypertension. Studies also indicate that cilnidipine displays better renal protection as compared to other antihypertensive drugs, including diuretics and other dihydropyridine CCBs. Neuroprotective effects were also elicited from animal studies. Cilnidipine has demonstrated a decrease in plasma level of beta-thromboglobulin, which is a marker of platelet activation able to prevent arterial thrombosis formation associated with increased sympathetic tone. The ability of cilnidipine to promote the metabolism of glucose is of clinical importance for treating hypertension along with insulin resistance. It also leads to improvement in insulin resistance in obese patients with hypertension [3, 6]. Cilnidipine was first approved in Japan in the year 2013 and is marketed in Japan under the brand name Atelec® (Ajinomoto Pharmaceuticals Co., Ltd.)[7]. Cilnidipine is practically insoluble in nature which affects the dissolution and absorption of the drug in the body leading to low bioavailability and limited efficacy with the oral tablet formulation [8]. To overcome the large particle size and the insoluble nature of the crystalline cilnidipine used in the currently available conventional products in India, we enhanced and converted the drug to aqueous soluble amorphous solid dispersion by super dissolution and absorption technology used by the Japan to obtain a product bioequivalent with the Atelec®. By using this technology in the new improved formulation of cilnidipine, our product now meets the standards set by Japanese Pharmacopoeia. We generated comparative dissolution data of improved formulation as compared to Atelec® and the conventional cilnidipine tablet from Indian brands (Table 1). The data demonstrated encouraging results showing improved formulation meets the Japanese standards used for Atelec®. However, the comparable Indian brand of cilnidipine tablet showed poor dissolution indicating that it did not meet the Japanese standards used for Atelec® tablet. Thus, based on the super dissolution data of improved formulation of cilnidipine, we conducted bioequivalence and bioavailability study with Atelec® and clinical and efficacy study with conventional cilnidipine tablet in India.

A. Bioequivalence: Improved Formulation in India Versus Atelec® in Japan market

The bioequivalence of Nexovas® versus Atelec® in Japan was assessed in an open-label. Balanced, analyst-blind, randomized, crossover bioequivalence study on 36 healthy, adult human subjects under fasting condition. The mean plasma concentration of the Nexovas® was similar to that of Atelec® (Fig. 1 and Table 2). The comparative mean pharmacokinetic data of Atelec® showed high intra-subject coefficient of variation >30% for primary pharmacokinetic parameter Cmax and less than 30% for primary pharmacokinetic AUC0-t & AUC0-∞. Thus, scaled average bioequivalence approach was used for the primary pharmacokinetic parameter Cmax and unscaled average bioequivalence approach for AUC0-t & AUC0-∞. Table 3 shows that for the parameter Cmax 95% upper bound confidence interval was less than 0 and the geometric mean ratio of test (Nexovas®)/reference (Atelec®) was within 80.00%-125.00% and for the parameter AUC0-t and AUC0-∞ the 90% confidence interval for the geometric mean ratio of test/reference was within 80.00%-125.00%; thus, demonstrating bioequivalence of Nexovas® and Atelec®. Using the above bioequivalent formulation of cilnidipine, we conducted a clinical study to assess and compare the efficacy and safety of Nexovas® versus the conventional cilnidipine tablets in the management of essential hypertension.

2. Clinical Efficacy and Safety Study

A. Materials and methods

This was a prospective, single-center, randomized, double-blind, double-dummy, parallel-group study to evaluate and compare the efficacy and safety of technologically improved formulation of cilnidipine 10 mg tablets (Nexovas®) with the conventional cilnidipine 10 mg tablets in patients with essential hypertension. We registered this trial prospectively in Clinical Trials Registry - India (CTRI) and the allocated CTRI number is CTRI/2021/03/031882. We included patients diagnosed with essential hypertension who required monotherapy treatment with cilnidipine 10 mg tablets as per investigator's discretion and in reference to treatment management provided in JNC 8 guideline. The goal BP was defined as <140/90 mmHg as per JNC8 guidelines [2].

1) Screening and eligibility criteria

Adult male or female patients aged 18 to 60 years (both ages inclusive) with essential hypertension (BP≥140/90 mmHg) and who require monotherapy with cilnidipine 10 mg tablets in the opinion of investigator were included in the study. The other criteria for inclusion were normal serum creatinine values and willingness to give their written informed consent to comply with all aspects of the protocol. Patients with BP≥180/110 mmHg; hypersensitivity to any ingredient of the investigational products; uncontrolled diabetes mellitus at screening (uncontrolled defined as patients with HbA1c more than or equal to 8% with or without treatment); symptomatic hypotension; uncontrolled kidney disease requiring dialysis or renal replacement therapy; apparent/pseudo hypertension due to white coat effect, and medical inertia; known history of heart failure, and reduced cardiac function; pedal edema, nephrotic syndrome, hypoproteinemia or microalbuminuria; history of clinically significant diseases or receiving any medication that would put the patient at risk during the study period, or would affect the study analyses; scheduled surgery during the study period; history of any interventional clinical trial within one month prior to screening; and history of alcohol and/or drug abuse and current significant alcohol consumption were excluded from the study. Female patients who are pregnant, lactating, or planning to conceive or not willing to use acceptable method of contraception were also excluded.

2) Treatment groups and dosing regimen

The investigational products in the study consisted of cilnidipine 10 mg tablets:

- *Test drug:* Nexovas® [Improved formulation of cilnidipine 10 mg tablets (of Macleods

Table 1
Percentage Drug Release - Invitro Dissolution as per Japanese Pharmacopoeia

Time in minutes	**Conventional Cilnidipine (India) (%)**	**Atelec® (Japan) (%)**	**Nexovas® (Macleods, India) (%)**
15	25.7	65.3	48.7
30	40.6	68.6	71.3
45	49.4	83.8	86.6
60	54.3	84.8	90.3
90	61.5	91	97.7
Dissolution in 0.1% polysorbate 80 in water 900 mL, paddle, 75 rpm			

Table 2.
Comparative Mean Pharmacokinetic Data of Atelec® and Nexovas® (Macleods, India)

Pharmacokinetic Parameters	**Atelec® (Japan)**			
	N	**Mean**	**Minimum**	**Maximum**
C_{max} (ng/mL)	68	12.94	3.02	42.92
AUC_{0-t} (ng.hrs/mL)	68	78.86	27.21	305.86
$AUC_{0-\infty}$ (ng.hrs/mL)	68	93.24	28.39	423.96
T_{max} (hrs)	68	2.17	0.75	5.00
$T_{1/2}$ (hrs)	68	17.02	4.49	42.13
K_e (hrs^{-1})	68	0.05	0.02	0.15
Pharmacokinetic Parameters	Nexovas® (Macleods, India)			
	N	Mean	Minimum	Maximum
C_{max} (ng/mL)	34	14.84	4.22	40.72
AUC_{0-t} (ng.hrs/mL)	34	89.40	31.69	321.46
$AUC_{0-\infty}$ (ng.hrs/mL)	34	113.12	32.80	556.51
T_{max} (hrs)	34	2.15	0.75	5.00
$T_{1/2}$ (hrs)	34	20.52	4.00	43.18
K_e (hrs^{-1})	34	0.04	0.02	0.17

AUC: Area under the curve; Cmax: Maximum plasma concentration; Ke: Elimination rate constant; N: Number of patients; SD: Standard deviation; Tmax: Time of maximum concentration; T1/2: Half-life of the drug.

Table 3.
Bioequivalence - Nexovas® (Macleods, India) versus Atelec® (Japan)

Pharmacokinetic Parameters	Intra Subject CV for Atelec® (%)	Ratio (T/R) (%)	95% Upper Bound	BE met (Yes/No)
C_{max}	30.74	115.37	-0.007	*Yes
AUC_{0-t}	17.74	112.19	0.007	†Yes
$AUC_{0-\infty}$	20.02	115.67	0.017	†Yes
AUC: Area under the curve; BE: Bioequivalence; C_{max}: Maximum plasma concentration; CV: Coefficient of variation *Ratio T/R should be between 80.00%-125.00% and 95% upper bound should be less than equal to zero. †Acceptable limits for 90% Confidence Interval 80.00%-125.00%				

Table 4.
Mean Change in Systolic and Diastolic Blood Pressure (mmHg) from Baseline to day 30 (±4 days) with Nexovas® (Macleods, India) Versus Conventional Cilnidipine (India)

	Systolic Blood Pressure (mmHg)			**Diastolic Blood Pressure (mmHg)**		
	Baseline	**Day 30**	**Mean Change**	**Baseline**	**Day 30**	**Mean Change**
Nexovas® (Macleods, India)	150	129	21	96	85	11
Conventional Cilnidipine (India)	150	134	16	98	89	9

Table 5.
Mean Change in Systolic and Diastolic Blood Pressure (mmHg) from Baseline to Day 15 (±4 days) with Nexovas® (Macleods, India) Versus Conventional Cilnidipine (India)

	Systolic Blood Pressure (mmHg)			**Diastolic Blood Pressure (mmHg)**		
	Baseline	**Day 15**	**Mean Change**	**Baseline**	**Day 15**	**Mean Change**
Nexovas® (Macleods, India)	150	139	11	96	87	9
Conventional Cilnidipine (India)	150	142	8	98	92	6

Pharmaceuticals)]

- *Active-comparator:* Conventional cilnidipine [Cilacar® 10 mg tablets (of J B Chemicals and Pharmaceuticals)]

Since Nexovas® and conventional cilnidipine were not identical in appearance, a dummy tablet (referred as placebo) was administered along with them. Hence, one tablet of cilnidipine 10 mg once daily orally for 30 days along with the dummy tablet of Nexovas® or conventional cilnidipine were administered.

3) Randomization

Patients were randomized as per a predetermined randomization schedule in equal ratio to the two treatment groups.

4) Statistical analysis

Analyses was performed using SAS® (statistical analysis system®) version 9.4 or above. The primary analysis was based on mean change of SBP from Baseline to Day 30 (±4 days).

Table 6.
Proportion of Patients Treated with Nexovas® (Macleods, India) and Conventional Cilnidipine (India) Achieving Goal Blood Pressure at Day 30 (±4 days) (End of Treatment)

	Proportion of Patients (%) Achieving Goal Blood Pressure at Day 30 (±4 days) (End of Treatment)	
	Systolic Blood Pressure	**Diastolic Blood Pressure**
Nexovas® (Macleods, India)	93.33	80.00
Conventional Cilnidipine (India)	80.00	53.33

Table 7.
Spot Urine-Protein Creatinine Ratio at Baseline and Day 30 (±4 days) in the Nexovas® (Macleods, India) and Conventional Cilnidipine (India) groups

	Spot Urine-Protein Creatinine Ratio at Screening	Spot Urine-Protein Creatinine Ratio at EOT	Percentage Reduction in Spot Urine-Protein Creatinine Ratio from Baseline to EOT
Nexovas® (Macleods, India)	0.19	0.16	15.79%
Conventional Cilnidipine (India)	0.20	0.18	10.00%

Within treatment comparison was performed by paired 't' test and between treatments comparison was performed by student's 't' test and analysis of covariance (ANCOVA).

3. Clinical Study Results

Thirty adult patients diagnosed with essential hypertension were included in this study and randomized 1:1 into the two treatment groups.

A. Primary outcome

Mean change in SBP and DBP from baseline to Day 30 (±4 days) (End of Treatment). The mean change in SBP and DBP was assessed in all the patients and the percentage reduction in BP was calculated as demonstrated in Table 4 and Fig. 2, respectively. Overall, the mean change from baseline to day 30 in systolic blood pressure (SBP) was found to be 21 and 16 mmHg and in diastolic BP (DBP) was found to be 11 and 9 mmHg with improved formulation of cilnidipine 10 mg tablet (Nexovas®) and conventional cilnidipine, respectively, which was statistically significant. As given in Fig. 2, the percentage reduction in SBP from baseline to day 30 (±4 days) was found to be 14% and 11.46% with Nexovas® and conventional cilnidipine, respectively. The percentage reduction in DBP from baseline to day 30 (±4 days) was found to be 10.67% and 9.18% with Nexovas® and conventional cilnidipine, respectively. Both the products indicated a statistically significant improvement (P<0.0001) in SBP and DBP from baseline to Day 30 (±4 days). However, there was no statistically significant difference in improvement between the two treatment groups, as analyzed by ANCOVA model and student't' test.

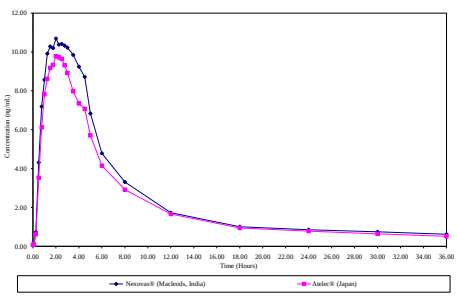

Fig. 1. Comparative Linear Plot of Cilnidipine Mean Plasma Concentration (ng/mL) versus Time (Hours)

B. Secondary outcomes

Mean change in SBP and DBP from baseline to Day 15 (±4 days). Mean change in SBP and DBP from baseline to day 15 (±4 days) of the treatment are indicated in Table 5. Proportion of patients achieving goal BP (<140/90 mmHg) at Day 30 (±4 days). Proportion of patients achieving goal BP at day 30 (±4 days) as per JNC 8 is given in Table 6 and Fig. 3.

1) Change in spot urine-protein creatinine (P/C) ratio

Presented below in Table 7. and Fig. 4. are the reduction in spot urine-protein creatinine ratio on Day 30 (±4 days) from baseline in Nexovas® and conventional cilnidipine groups.

C. Safety Outcome

No significant adverse event was reported in any of the treatment group indicating that cilnidipine is safe for use in patients with hypertension.

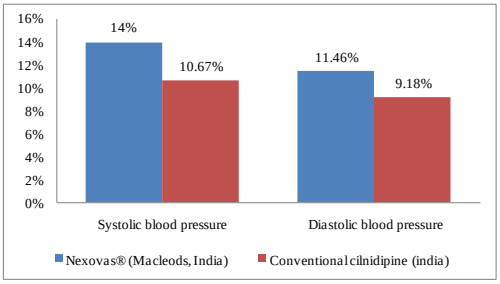

Fig. 2. Percentage reduction in blood pressure (BP) at Day 30 (±4 days) (End of Treatment)

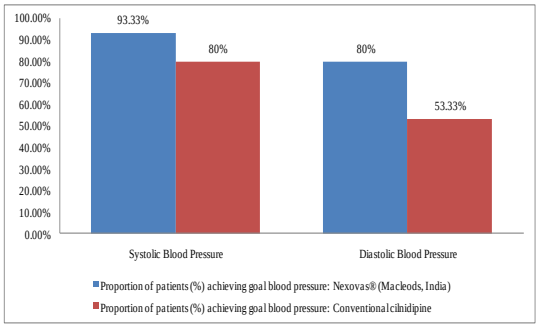

Fig. 3. Proportion of Patients Treated with Cilnidipine 10 mg Tablets Achieving Goal Blood Pressure at Day 30 (±4 days) (End of Treatment)

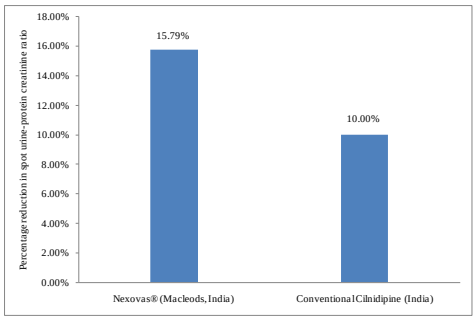

Fig. 4. Percentage reduction in Spot Urine-Protein Creatinine Ratio from Baseline to Day 30 (±4 days)

4. Discussion

The dissolution data of the improved formulation Nexovas® was superior to the conventional cilnidipine in India and Nexovas® dissolution was comparable to Japanese standards. The effectiveness of an oral dosage form depends upon the intrinsic ability of the drug to dissolve in the fluids of the gastrointestinal tract prior to being absorbed into the circulation. Therefore, the rate of dissolution of a drug is important for its bioavailability and therapeutic effectiveness. Any change in drug dissolution will significantly affect the bioavailability. Nexovas® demonstrated bioequivalence with the Atelec® for the rate and extent of absorption, as assessed by the pharmacokinetic parameters of Cmax, AUC0-t, and AUC0-∞. It also demonstrated efficacy and safety in clinical study conducted in patients with essential hypertension. In the clinical study, a statistically significant reduction in both SBP and DBP was observed from baseline to Day 30 in both the treatment groups (P<0.0001). Numerically, better improvement was noted in Nexovas® group. At the end of the study, a higher proportion of patient in the Nexovas® group achieved goal SBP and DBP. In addition, there was a better mean improvement in BP on day 15 in patients treated with Nexovas® than those treated with conventional cilnidipine. The spot urine-protein creatinine ratio also demonstrated a numerically higher reduction with Nexovas® than with conventional cilnidipine.

The clinical efficacy of the Nexovas® demonstrated better results in the following parameters when compared with conventional cilnidipine:

- 14% reduction in SBP compared to 10.67% reduction with the conventional cilnidipine
- 11.46% reduction in DBP compared to 9.18% reduction with conventional cilnidipine
- Mean changes in SBP from baseline to EOT with the Nexovas® and conventional cilnidipine were 21 mmHg and 16 mmHg, respectively.
- A 22.22% better result was obtained in DBP from baseline to EOT with the Nexovas®.
- The systolic goal BP was achieved in 93.33% of patients in the Nexovas® group, where as it was achieved in 80.00% patients in the conventional cilnidipine group.
- The diastolic goal BP was achieved in 80.00% of patients in the Nexovas® group, where as it was achieved in 53.33% patients in the conventional cilnidipine group.

Thus, our new improved formulation of Cilnidipine had superior dissolution pointing towards superior bioavailability and statistically higher improvement in blood pressure after 1 month of treatment.

5. Conclusion

The improved formulation of cilnidipine 10 mg (Nexovas®) demonstrated super dissolution when compared to the conventional cilnidipine, was bioequivalent to Atelec®, and in clinical efficacy and safety trial showed statistically significant improvement in BP after one month of treatment. Goal BP (<140/90 mmHg) was achieved in higher proportion of patients treated with the Nexovas® compared to the conventional cilnidipine in India.

6. Declarations

- *Funding:* This study was entirely funded by Macleods Pharmaceuticals Ltd.
- *Conflict of interest*: All authors are full-time employees of Macleods Pharmaceuticals Ltd.
- *Ethical approval*: This study was approved by Ethics Committee.

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