ATELEC® Tablets 10

1. Name of the medicinal product

1.1 Product name
ATELEC Tablets 10

1.2 Strength
Each film-coated tablet contains 10mg of cilnidipine

1.3 Pharmaceutical dosage form
Film-coated tablet

2. Quality and quantitative composition

2.1 Qualitative declaration
Cilnidipine (INN)

2.2 Quantitative declaration
Each film-coated tablet contains 10mg of cilnidipine

3. Pharmaceutical form
ATELEC Tablets 10 is a white oval film-coated tablet with cleavage line.

Brand name	Identification code	Appearance			Size and average weight
		Face	Reverse	Lateral	
ATELEC Tablets 10	AJI 10				MjA: ca. 12.3 mm MnA: ca. 6.0 mm T : ca. 4.7 mm W : ca. 0.27 g

T: thickness; W: weight; MjA: major axis; and MnA: minor axis

4. Clinical particulars

4.1 Therapeutic indication
ATELEC is indicated for the treatment of hypertension.

4.2 Posology and method of administration
Usually, for adults, 5 to 10 mg is administered as cilnidipine for orally once a day after breakfast. The dosage may be adjusted according to the patient's age and symptoms. The dose can be increased up to 20 mg once a day, if a sufficient response does not appear. For adults with severe hypertension, ATELEC should be administered 10 to 20 mg once a day for oral use after breakfast.

4.3 Contraindication
Patients with hypersensitivity to the active substance or to any of the excipients.
Pregnant women or women having possibilities of being pregnant (See "Pregnancy and lactation" section).

4.4 Special warning and precautions for use
Careful Administration (ATELEC should be administered with care in the following patients.)
(1) Patients with serious hepatic dysfunction [The plasma concentration may become elevated.]
(2) Patients with a history of serious adverse reactions to calcium antagonists
(3) Elderly patients [See "Use in the Elderly" section]

Important Precautions
As it has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of ATELEC is necessary, the dosage should be gradually decreased under close observation.
If ATELEC is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
Direct the patient not to discontinue this drug without physician's instructions.

Use in the Elderly
ATELEC should be administered carefully under close observation of the patient's condition, taking such measures as starting with a lower dose (e.g. 5mg).
Use in the Elderly is generally acknowledged that the excessive hypotensive action should be avoided in the elderly.
Therefore, adverse reactions (including abnormalities in laboratory data) in the elderly aged 65 years and over, were observed in 152 of 2,863 patients in the investigation at the time of approval and the postmarketing studies (at the end of the reexamination period) .

Pediatric Use
The safety of ATELEC in pediatric patients has not been established (no clinical experience).

Precautions concerning Use
When dispensing the drug:
It should be clarified that the patient understands that the tablets must first be removed from the PTP blister package before they are ingested. [It is reported that, in case of the ingestion of the PTP blister package, the sharp hard edges of the package can easily perforate the esophageal mucosa and result in serious complications, such as mediastinitis.]

4.5 Interaction with other medicinal products and other forms of interactions
ATELEC is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19.

Precautions for Coadministration (ATELEC and the following drugs should be coadministered with care.)

Names of Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Agents with hypotensive effect	There is a possibility that blood pressure is excessively decreased.	Drug action is considered to be enhanced additively or synergistically.
Digoxin	It has been reported that some other calcium antagonists (e.g., nifedipine) increased the plasma concentration of digoxin. If any toxic signs/symptoms attributable to digoxin (e.g., nausea, vomiting, headache, abnormal vision, arrhythmia) are observed, appropriate measures should be instituted such as digoxin dose adjustment or discontinuation of ATELEC, depending on the patient's condition.	The mechanism is not completely clarified yet, but is thought to lie in decreased renal and extrarenal clearances.
Cimetidine	It has been reported that effects of some other calcium antagonists (e.g., nifedipine) were enhanced.	It is thought that cimetidine decreases hepatic blood flow with the consequent suppression of the emzymatic metabolism of calcium antagonists in liver microsomes, and at the same time cimetidine lowers gastric acid output and thus increases absorption of calcium antagonists.
Rifampicin	It has been reported that effects of other calcium antagonists (e.g., nifedipine) were reduced.	It is generally thought that hepatic drug-metabolizing enzyme (cytochrome P-450) induced by rifampicin facilitates metabolism of calcium antagonists and thus increases the clearance of these agents.
Antifungal azoles: Itraconazole, miconazole, etc.	The blood concentration of ATELEC may be elevated.	Antimycotic azoles are thought to inhibit CYP3A4, a drug-metabolizing enzyme for ATELEC.
Grapefruit juice	It has been demonstrated that the plasma concentration of ATELEC is elevated.	Details of the underlying mechanism remain to be elucidated, but some constituents in grapefruit juice may inhibit CYP3A4, a drug-metabolizing enzyme for ATELEC.

4.6 Pregnancy and lactation
ATELEC should not be administered to pregnant women or women having possibilities of being pregnant. [It has been reported that ATELEC prolongs the gestation period and delivery time in animal experiments (in rats).]
It is advisable to avoid the administration of ATELEC to nursing mothers. However, if the administration is indispensable, the patient should be instructed to discontinue lactation. [Transfer of this drug to mother's milk has been reported in animal experiments (in rats).]

4.7 Effects on ability to drive and use machine
The symptoms, such as dizziness may occur because of the hypotensive action from this drug. Give warning against engaging in hazardous activities requiring alertness, such as working at a height, operating machinery or driving motor vehicles.

4.8 Undesirable effects
Adverse reactions, including abnormalities in laboratory data, were observed in 414 (6.95%) of 5,958 patients in the investigations at the time of approval and the postmarketing studies (at the end of the reexamination period).

Clinically significant adverse reactions
1) Hepatic dysfunction and jaundice (frequency unknown): Hepatic function disorder and jaundice accompanied with increased AST (GOT), ALT (GPT) and γ-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of ATELEC, should be taken.
2) Thrombocytopenia (incidence: <0.1%): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of ATELEC, should be taken.

Other adverse reactions
If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

	0.1 to <5%	<0.1%	Incidence unknown
Hepatic[Note 1)]	Increases in AST (GOT), ALT (GPT), LDH, etc.	ALP increased	
Renal	Increases in creatinine or urea nitrogen, urinary protein positive	Urinary sediment present	
Psychoneurological	Headache, headache dull, dizziness, dizziness on standing up, shoulder muscle stiffness	Sleepiness, insomnia, tremor finger, forgetfulness	Numbness

Cardiovascular	Flushed face, palpitation, feeling hot, electrocardiogram abnormal (ST depressed, inverted T waves), blood pressure decreased	Chest pain, cardiothoracic ratio increased, tachycardia, atrioventricular block, feeling cold	Extrasystole, bradycardia
Gastrointestinal	Nausea, vomiting, abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhoea	
Hypersensitivity[Note 2)]	Rash	Redness, itching	Photosensitivity
Hematologic	Up or down in WBC, neutrophils and hemoglobin	Up or down in RBC, hematocrit, eosinophils and lymphocytes	
Other	Oedema (facial, lower leg, etc.), general malaise, pollakiuria, increased serum cholesterol, up or down in CK (CPK), uric acid, serum K and serum P	Feelings of weakness, gastrocnemius muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, up or down in fasting blood sugar, total protein, serum Ca and CRP, cough	Tinnitus

Note 1): The patient should be carefully monitored for these symptoms, and if any abnormality is noted, ATELEC should be discontinued.
Note 2): If any such symptom appears, ATELEC should be discontinued.
Inform your doctor of undesirable effects occurred during the use of drug.

4.9 Overdose
Overdosage of ATELEC may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken. Hemodialytical removal of the drug is not effective because of its high rate of protein binding.

5. Pharmacological properties

5.1 Pharmacodynamic properties

1. Antihypertensive Effect

(1) In various hypertensive animal models (spontaneously hypertensive rats, renal hypertensive rats and dogs, DOCA salt hypertensive rats, and stroke-prone spontaneously hypertensive rats), a single oral dose of cilnidipine showed a gradual and long-lasting hypotensive action that was dose-dependent at 1mg/kg or more. In contrast, it showed a weak hypotensive action in normotensive rats. The duration of the action was not prolonged by an excessive dosage. In renal hypertensive dogs, cilnidipine showed an additive effect when coadministered with a β-blocker or an angiotensin-converting enzyme inhibitor.

(2) In stroke-prone spontaneously hypertensive rats and renally hypertensive dogs, repeated oral doses of cilnidipine had a stable hypotensive action which did not show attenuatetion. Discontinuation of cilnidipine did not cause a rebound in blood pressure.

(3) In conscious and unrestrained spontaneously hypertensive rats, cilnidipine did not increase the heart rate during hypotension. Cilnidipine did not increase the plasma noradrenaline level during hypotension, nor did it cause a significant decrease, which an adrenergic blocker (guanethidine sulfate) did. Cilnidipine did not cause orthostatic hypotension, although a ganglion blocker (pentolinium) did in a tilt test using rabbits.

(4) In patients with essential hypertension, a single daily dose of cilnidipine showed a hypotensive action that maintained for 24 hours and was still evident early in the next morning. Power spectral analysis of the R-R intervals of 24 hours electrocardiogram revealed that cilnidipine did not increase sympathetic activity or the heart rate as a reflex response to the reduction of blood pressure.

2. Inhibitory action on Stress induced Pressor Response

(1) In conscious and unrestrained spontaneously hypertensive rats, cilnidipine inhibited the elevation of blood pressure and plasma norepinephrine levels induced by cold stress. Cilnidipine also inhibited the elevation of blood pressure induced by air jet stress (mental stress) in rats.

(2) In healthy adult male volunteers whose blood pressure was elevated by 20% or more in cold stress test, cilnidipine suppressed the elevation of blood pressure induced by cold stress.

3. Inhibitory action on Sympathetic Stimulation induced Pressor Response

(1) In pithed spontaneously hypertensive rats, cilnidipine supressed the elevation of blood pressure induced by electrical sympathetic stimulation.

(2) In isolated and perfused mesenteric arterial vascular preparation in spontaneously hypertensive rats, cilnidipine also inhibited the release of norepinephrine induced by electrical sympathetic stimulation.

4. Effect on Cerebral Circulation

(1) In spontaneously hypertensive rats, cilnidipine did not decrease cerebral blood flow even if the dose which decrease blood pressure by 30-40% in rats was administered. The autoregulation of cerebral blood flow was satisfactorily maintained while the blood pressure was decreased.

(2) In hypertensive patients comlicated by cerebrovascular disease, the cerebral blood flow was maintained while blood pressure was lowered.

5. Effects on Cardiac Function

(1) In dogs, cilnidipine decreased heart rate and myocardial contractility at a higher dose than that inducing an increased flow of arterial blood.

(2) In anesthetized open chest dogs, cilnidipine decreased the myocardial oxygen consumption at dose inducing hypotension. At the time, it neither caused tachycardia nor affected cardiac contractility.

(3) In patients with essential hypertension, cilnidipine did not affect heart rate while the blood pressure was decreased and in patients with abnormal cardiothoracic ratio (CTR), it improved the CTR.

6. Effects on Renal Function

(1) In anesthetized spontaneously hypertensive rats, cilnidipine increased the urinary volume, renal blood flow and glomerular filtration rate at the dose inducing hypotension. Cilnidipine also increased the urinary volume, renal blood flow and glomerular filtration rate, when the renal function was depressed by endothelin.

(2) In patients with essential hypertension, cilnidipine did not affect renal function while the blood pressure was decreased.

7. Effect on Cardiovascular Disturbance Associated with Hypertension

(1) In stroke-prone spontaneously hypertensive rats, a single daily dose of cilnidipine suppressed the appearance of stroke and improved the survival rate. In addition, it lessened cardiac hypertrophy (increased heart weight), thickening of the ventricular wall, myocardial fibrosis and lesions in the kidney. Moreover, it depressed medial thickening in the coronary arterial wall and decreased calcium content in the aorta.

(2) In patients with essential hypertension, cilnidipine decreased the atherosclerotic index and serum lipid peroxide.

8. Mechanisms of Action

(1) Experimental data suggest that cilnidipine binds to the dihydropyridine binding sites of L-type voltage dependent calcium channel and inhibits Ca^{2+} influx across the cell membranes of vascular smooth muscle cells via this channel (rabbits *in vitro*).
Consequently, vascular smooth muscle is relaxed, causing vasodilation. Through this mechanism, cilnidipine is considered to have an hypotensive action.

(2) Cilnidipine inhibits Ca^{2+} influx via N-type voltage dependent calcium channels in the sympathetic nerve cell membrane. The inhibition of Ca^{2+} influx via N-type voltage dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage dependent Ca^{2+} channels (rats *in vitro*).
Consequently, release of norepinephrine from sympathetic nerve terminals would be inhibited. Cilnidipine is considered to suppress the reflex increase in heart rate which may be mediated by sympathetic activation after blood pressure reduction and to inhibit stress-related hypertension through this mechanism.

5.2 Pharmacokinetic properties

1. Plasma Drug Levels

When a single dose of 5 mg, 10mg or 20mg cilnidipine was orally administered to six healthy male volunteers, the C_{max} was found to be 4.7 ng/mL, 5.4 ng/mL and 15.7 ng/mL, respectively, and the $AUC_{0\text{-}24}$ to be 23.7 ng·hr/mL, 27.5 ng·hr/mL and 60.1 ng·hr/mL, respectively. Thus, both parameters increased in a dose-dependent manner.
When a single dose of 10 mg of cilnidipine was repeatedly administered once a day to six healthy male volunteers, pharmacokinetic parameters of cilnidipine were indicated as follows. The plasma concentration reached a steady state from Day 4 of the administration and there was no evidence of the accumulation.

Parameter Day of dosing	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (α) (hr)	$T_{1/2}$ (β) (hr)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)
Day 1	9.5±1.6	2.8±1.0	1.0±0.2	5.2±2.0	51.4±12.7
Day 4	13.5±5.0	3.7±0.8	–	–	101.8±29.0
Day 7	16.5±7.9	3.0±1.3	1.1±0.6	8.1±2.7	95.5±34.5

(Mean ± S.D.)

The pharmacokinetics of this drug have also been evaluated in patients with impaired renal function (serum creatinine:1.5-3.1mg/dL) following a single oral dose of 10mg in the hypertensive patients, and no significant differences were found in the pharmacokinetic profile of this drug compared with that in patients with normal renal function.
Repeated oral administration of this drug at a dose of 10mg once a day for 7days in patients with impaired renal function caused no differences in the pharmacokinetic profile compared with that in patients with normal renal function.

2. Metabolism and Excretion

From the metabolites identified in the plasma and urine of healthy male volunteers, it is considered that the major route of cilnidipine metabolism is demethylation of the methoxyethyl group followed by hydrolysis of the cinnamyl ester and oxidation of the dihydropyridine ring. It is considered that CYP3A4 is mainly involved and CYP2C19 is partly involved in the demethylation of the methoxyethyl group (*in vitro*).
The calcium channel blocking action of the metabolite with the demethylated methoxyethyl group was only 1/100 of that of the parent compound (in rabbits).
When a single oral dose of 10mg of cilnidipine was repeatedly administrated to healthy male volunteers once a day for 7days, no unchanged compound of cilnidipine but 5.2% of the dose was excreted in the urine as metabolites. (The approved administration of ATELEC is orally once a day after breakfast.)
An *in vitro* experiment showed that cilnidipine was 99.3% bound to human serum protein.

5.3 Preclinical safety data

In studies on acute toxicity, subacute toxicity, chronic toxicity, reproduction, antigenicity, mutagenicity, carcinogenicity, and general pharmacology to evaluate the safety of cilnidipine, there was no finding of particular concern.

6. Pharmaceutical particulars

6.1 List of excipient
Lactose Hydrate, Microcrystalline Cellulose, Macrogol 400, Magnesium Aluminometasilicate, Croscarmellose Sodium, Hydroxypropylcellulose, Hypromellose Phthalate, Talc, Magnesium Stearate, Hypromellose, Ethylcellulose, Macrogol 6000, Macrogol 600, Titanium Oxide and Carnauba Wax.

6.2 Incompatibilities
Since ATELEC tablets 10 is a tablet preparation, it is not applicable

6.3 Shelf life
36 months from manufacturing date

6.4 Special precautions for storage
Store below 30°C, protect from light.

6.5 Nature and contents of container
Blister: CPP, Aluminum

7. Name and address of importer

DKSH (Thailand) Limited
Bangkok, Thailand

8. Thai registration number

1C 9/61 (NC)

9. Date of authorization

3 April 2018

10. Date of revision of the text

4 June 2018