Azelnidipine Tablets IP 8 mg / 16 mg

AZOVAS® 8

COMPOSITION

Each uncoated tablet contains:

Azelnidipine IP..... 8 mg

Excipients ..... q.s.

AZOVAS® 16

COMPOSITION

Each uncoated tablet contains:

Azelnidipine IP..... 16 mg

Excipients ..... q.s.

DOSAGE FORM:

Tablets

INDICATIONS:

Essential hypertension; Stage I and Stage II Hypertension

DOSE AND METHOD OF ADMINISTRATION:

Usually, Azelnidipine 8 ~ 16 mg in adults administered orally once after breakfast daily. It is to be noted that start the administration with a low dose or even with a single 8 mg tablet, dose should be adjusted according to the symptoms, up to 16 mg per day.

USE IN SPECIAL POPULATIONS:

Pregnant and lactating women

Should not be administered to women who may possibly be pregnant or are pregnant. [Increase in pre-implantation and post- implantation embryo mortality were observed during the administration to pre-pregnancy - initial animal studies (in rats), weight loss of offspring, extension of delivery time and gestation period has been found. In addition, extension of the delivery time and the gestation period has been observed due to administration of late pregnancy].

Avoiding administration to lactating women is desirable; feeding should be stopped when administration is unavoidable. [Secretion of this drug in the breast milk has been reported in rats].

Elderly

When used in elderly, start the administration with low dose or even 8 mg, administered carefully while observing the full course is desirable. [In the elderly, there is a possibility that the cerebral infarction occurs, due to excessive and undesirable hypotension in general].

Children

Never Use; Safety for low birth weight infants, newborns, infants and children has not been established.

CONTRA-INDICATIONS:

Azelnidipine should not be administered in the following patients:

- Women who may possibly be pregnant or are pregnant (See section "Use in Special Population").
- Patients with a history of hypersensitivity to any component of this drug.
- If combined with azole antifungals, (Itraconazole, Miconazole, etc.), HIV protease inhibitors (Ritonavir, Saquinavir, Indinavir, etc.) (See section "Drug interaction").

WARNINGS & PRECAUTIONS:

- **Careful administration (It should be administered with caution in the following patients.)**
  - Patients with serious liver and kidney dysfunction. The drug is metabolized in the liver. Also in patients with severe renal dysfunction in general, there is a possibility that the renal function is reduced.
  - Elderly (See section "Use in Special Population")
- **Important Precautions**
  - When administration of calcium antagonists stopped abruptly, it have been reported that patients develop symptoms, which reduced gradually when with washout of the drug, it should be carefully monitored. Also, be careful not to stop the medication without a physician's supervision to the patient.
  - Because with the administration of this drug there is a risk of excessive decrease of pressure in rare cases, make appropriate measures such as dose reduction or withdrawal from medication in such cases.
  - Because it may cause dizziness based on the hypotensive effects, take precautions when working with dangerous operation of aerial work, automotive and machinery.
  - Myocardial infarction, arrhythmia and heart failure (atrial fibrillation, etc.) have been reported during treatment with this drug, though causal relationship is not clear.
  - It has been reported that dialysis effluent of CAPD (continuous ambulatory peritoneal dialysis) patients becomes clouded, it is important to note the differential diagnosis from peritonitis, etc.

DRUG INTERACTIONS:

This drug, is mainly metabolized by the cytochrome P450 3A4 (CYP3A4) (see section "Pharmacokinetics").

- **Combination contraindicated (Do not use)**

Drug name, etc.	Clinical symptoms and Treatment	Mechanism and Risk Factors
Azole antifungal agents Itraconazole Miconazole, etc.	It has been reported that the AUC of this drug is increased to 2.8-fold by combination with Itraconazole.	These drugs inhibit CYP3A4, thus lowered the clearance of this drug.
HIV Protease Inhibitor Ritonavir, Saquinavir, Indinavir, etc.	There is a possibility that the action of the drug is enhanced by the combination.	

- **Use with Caution (Note the combination)**

Drug name, etc.	Clinical symptoms and Treatment	Mechanism and Risk Factors
Other antihypertensive agents	There is a possibility that excessive hypotension may occur. Reduce dose of this drug or other antihypertensive agents if necessary.	Pharmacological effect is enhanced by the combined use of antihypertensive agents of different mechanism of action.
Digoxin	It has been reported by the combined use with digoxin Cmax and AUC is increased by 1.3 to 1.5 times. Decrease the amount of digoxin if necessary.	It is considered that it inhibits the renal excretion of Digoxin (renal tubular secretion) and external excretion from the kidneys.
Cimetidine Imatinib mesylate Delavirdine mesylate Macrolide antibiotic Erythromycin, Clarithromycin, etc.	There is a possibility that the action of the drug is enhanced by the combination. Cease the administration of these drugs or reduce the dose of this drug if necessary.	These drugs inhibit CYP3A4, thus lowered the clearance of this drug.
Simvastatin	The AUC of Simvastatin is increased to 2.0 times by the combined use. Cease the administration of Simvastatin or this drug if necessary.	These drugs competitively inhibit CYP3A4, considered to decline clearance of each other. Patients with impaired renal function should take special attention.
Cyclosporine Benzodiazepines Diazepam, Midazolam, Triazolam, etc. Oral Birth control pills, Follicular, Luteinizing hormones, etc.	There is a possibility that the action of these drugs or this drug is enhanced by the combined use. To reduce the dose of these drugs or of this drug if necessary.	These drugs competitively inhibit CYP3A4, considered to decline clearance of each other.
Tandospirone citrate	There is a possibility that the action of this drug is enhanced by the combination. Cease the administration of Tandospirone citrate or decrease the amount of this drug if necessary.	Blood pressure lowering effect of the central nervous system through the serotonin receptor enhances the hypotensive action.
Rifampicin, Phenytoin, Phenobarbital	It is believed that by metabolic enzyme induction effect of these drugs, clearance of this drug increases.	It is believed that the metabolic enzyme induction effect of these drugs increase the clearance of this drug.
Grapefruit juice	The blood concentration of this drug increases. Since there is a possibility that the hypotensive effect is enhanced, patient should be careful not to drink grapefruit juice while taking this drug.	This is probably because the components contained in grapefruit juice inhibit the metabolism of this drug by CYP3A4, to reduce the clearance.

UNDESIRABLE EFFECTS:

- **Clinically significant adverse reactions (incidence unknown[1])**

Liver dysfunction, jaundice: Because it might cause liver dysfunction there may be rise in AST (GOT), ALT (GPT), or γ-GTP, patient should be carefully monitored, administration of this drug should be discontinued if any abnormalities are observed, and appropriate measures should be taken.

Atrioventricular block, sinus arrest, bradycardia: Because it may cause atrioventricular block, sinus arrest, bradycardia may occur, administration of this drug should be discontinued in the case of abnormal dizziness, such as fluctuation, and appropriate measures should be taken.

- **Other side effects**

Since following side effects may appear, take appropriate measures if any abnormalities are found such as discontinuing administration.

	Less than 0.1-1%	Less than 0.1%	Incidence unknown Note [1]
Hypersensitivity[2]	Rash	Itching	Angioedema
Neuropsychiatric	Headache, heaviness of the head, Light headedness, Dizziness	Drowsiness	
Digestive organ	Stomach discomfort, nausea	Constipation, abdominal pain, diarrhea	Gingival hypertrophy, Stomatitis
Circulatory organ	Palpitations, hot flashes, Hot flushes		
Blood		Eosinophilia	
Liver	ALT (GPT) elevation, AST (GOT) rise, LDH rise, γ-GTP rise, Abnormal liver function, ALP rise	Total bilirubin Rise	
Urinary organs	BUN increased	Creatinine rise, Increase urine, Frequent urination	
Other	Uric acid increased, Increased total cholesterol, CK (CPK) increased, Potassium increased, malaise, (Floating feeling, feeling abnormal sense of Defect etc.)	Potassium decreased, Edema, Numbness	Chylous ascites[3]

1. Incidence unknown because the side effects are observed in spontaneous reporting.
2. Administration of this product should be discontinued. Further, photosensitivity has been reported in analogous drugs.
3. It is easy to occur in patients with hypoalbuminemia.

Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE:

No data available. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES:

Pharmacodynamics:

Azelnidipine is less susceptible to hepatic first-pass effect, antihypertensive effect is slow sustained.

Hypotensive action

The 0.1 to 1 ~ 3 mg / kg of this drug lowered blood pressure in a dose-dependent manner by a single oral dose in hypertensive animal model (spontaneously hypertensive rats, DOCA salt hypertensive rats, Renal hypertensive rats, Perinephritis renal hypertension dog), its action is sustained and expressed slowly, it had little effect on the heart rate compared to similar drugs.

In addition, hypotensive action was stable after repeated oral administration to renal hypertensive dogs or spontaneously hypertensive rats.

Mechanism of action

This drug expresses hypotensive action by L-type Ca channel antagonism and blood vessels dilation. In receptor binding experiments using pig heart microsomes, 50% inhibitory concentration (IC_{50} value) and inhibition constant (Ki values) for the specific binding of 3 H-nitrendipine was 3.1nM and 2.1nM respectively.

Pharmacokinetics:

Absorption

As a result of once 7 consecutive days oral-day administration of Azelnidipine 8 mg tablets in six cases of a healthy adult male, time to reach maximum plasma concentration was 2 to 3 hours,

half-life was 19-23 hours. Plasma concentrations 24 hours after administration, showed a nearly constant value from the second day of administration, and reached to steady state quickly. AUC0-∞ and C_{max} of fasting administration was 69% and 38%, respectively, compared to administration after a meal.

Plasma concentrations of the unchanged drug in the case of a once seven consecutive days oral administration of 8 mg tablets Azelnidipine (after a meal administration)

Dose	Day of administration	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	AUC_{0-24} (ng.hr/mL)
8mg	Day 1	11.8 ± 1.4	3.2 ± 0.3	1.3 ± 0.2	23.1 ± 8.1	59.7 ± 6.9
	Day 7	14.7 ± 1.6	2.2 ± 0.3	1.0 ± 0.1	19.2 ± 2.2	81.6 ± 13.4

n = 6, Mean ± SE

As a result of a single oral dose of 8 mg Azelnidipine tablets after breakfast in six mild-moderate essential hypertension patients, time to reach peak plasma concentration was 3.7 hours, C_{max} 9.4 ng/ml, half-life (monophasic) 6.1 hours and AUC_{0-24} was 66.5ng • hr / ml. Plasma concentration was considered to levels similar to healthy adults.

Plasma protein binding rate

In vitro plasma protein binding rate of this drug is 90-91%, and non-specific binding is with lipoproteins mainly.

Metabolism

The main metabolic sites are liver and small intestine, dihydropyridine ring is oxidized by CYP_3A_4.

Excretion

In data from studies, it was found that after a single oral dose of 4 mg 14C-Azelnidipine to four healthy adult male, the total administered radioactivity excretion rate to the feces and urine up to 7 days after administration, was 26% in urine and the 63% in feces.

Pharmacokinetics in liver dysfunction patients

In data of foreign studies, it was found that after a single oral dose of 8 mg Azelnidipine tablet in eight healthy people and mild to moderate liver dysfunction patients, changes in the plasma concentration were similar.

Target	$C^{Note)}_{max}$ (ng/mL)	$AUC^{Note)}_{0-\infty}$ (ng.hr/mL)	CL/F (mL/min)
Patients with impaired liver function	6.0	52.8	3152.5 ± 2342.2
Healthy human	8.2	68.0	2345.2 ± 1449.1

n = 8, Mean ± SD, Note) Geometric mean

Pharmacokinetics in renal function declined hypertensive patients

As a result of 8 mg Azelnidipine once daily seven consecutive days oral administration after breakfast in six cases of hypertension patients with reduced renal function (serum creatinine 1.5 ~ 5.3mg/dL), maximum plasma concentration after day 1 and day 7 administration were 8.6ng/mL and 17.1ng/mL, AUC_{0-24} was 67.3ng • hr / mL and 154.5ng • hr / mL showed a large significantly value

at 7 days, plasma concentration reached a steady state 24 hours after administration and had a value substantially constant after day 6.

Days of administration	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-24} (ng.hr / mL)
Day 1	8.6 ± 0.87	4.7 ± 0.67	9.1 ± 1.34	67.3 ± 5.81
Day 7	17.1 ± 2.08$^{\#1)}$	3.5 ± 0.56	19.7 ± 4.86	154.5 ± 17.79$^{\#1)}$

n = 6, Mean ± SE, $^{\#1)}$: p<0.01 (paired t-test)

Pharmacokinetics in elderly

As a result of 8 mg Azelnidipine once daily seven consecutive days oral administration after breakfast in five elderly hypertensive patients (65-84 years), maximum plasma concentration arrival time of day 1 and day 7 administration were 4.4 hours and 3.2 hours, respectively, with a half-life of 6.4 hours and 8.6 hours, respectively, AUC_{0-24} was 107.0ng • hr / mL and 242.8ng • hr / mL,

respectively, AUC_{0-24}, peak plasma concentration and half-life showed significantly large value on day 7, plasma concentration

reached a steady state 24 hours after administration and had a value substantially constant after day 7.

Days of administration	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-24} (ng.hr / mL)
Day 1	15.8 ± 2.1	4.4 ± 1.0	6.4 ± 1.7 $^{\#1)}$	107.0 ± 16.9
Day 7	25.7 ± 3.6$^{\#2)}$	3.2 ± 0.5	8.6 ± 1.6 $^{\#2)}$	242.8 ± 48.8 $^{\#2)}$

n = 5 ($^{\#1)}$ n = 4), Mean ± SE, $^{\#2)}$: p<0.05 (paired t-test)

PACKAGING INFORMATION:

Blister of 4 Tablets & 10 Tablets.

STORAGE:

Store below 25 °C. Protect from light and moisture.

Keep out of reach of children.

Marketed by & ®Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

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Note: This prescribing information is applicable for India Market only