For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

UNIAZ

1. Generic Name

Azelnidipine Tablets I.P 8 mg and 16 mg

2. Qualitative and quantitative Composition:

Each uncoated tablet contains:

Azelnidipine I.P….. 8 mg/16 mg

Excipients…… q.s.

The excipients used are Lactose, Starch, Crospovidone, Polysorbate 80, Isopropyl alcohol, Colloidal silicon dioxide, Magnesium stearate, Low substituted Hydroxy propyl methyl cellulose.

3. Dosage form and strength

Dosage form: Uncoated tablets

Strength: Azelnidipine 8 mg and 16 mg

4. Clinical particulars

4.1. Therapeutic indication

UNIAZ 8 For the treatment of Stage – I Hypertension.

UNIAZ 16 For the treatment of Stage – II Hypertension

4.2. Posology and method of administration

Normally, UNIAZ must be used orally only one time after breakfast for an adult. In addition, start the dosage from 8mg or still further low dosages one time and based on the symptoms the dosage must be increased or decreased appropriately but the maximum dosage per day shall be up to 16 mg.

4.3. Contraindications

- Hypersensitivity to active ingredients or to any of the excipients.
- Pregnant women or women who has a possibility to conceive.
- Patients who are using Azole antifungal drug (Itraconazole, Miconazole etc), HIV Protease inhibitor (Ritonavir, Saquinavir, Indinavir etc.).

4.4. Special warnings and precautions for use

Must be used with caution towards the:

- Patients who are having serious Liver/Kidney function failure (This drug will metabolize in the Liver. Further, generally for the patients who are having a serious Kidney function failure, there is a possibility of pressure drop along with the decrease in kidney function)
- Aged individual

Important and basic instructions:

- When the intake of calcium antagonists is suspended suddenly, in case of discontinuation of this product, gradual dose reduction should be made and conduct sufficient observations since there are cases where it is reported that the symptoms are worsening. Further, it must

be instructed to patients that the drug must not be discontinued without any direction unless until given by the physician.

- There are possibilities of the occurrence of excessive low blood pressure very rarely due to the intake of this drug, therefore, in that case please take appropriate measures such as reducing the dosage or discontinuing the intake of the drug.
- Must be cautious while working at heightened place, travelling in train, operating with machines which are dangerous since giddy feeling can be felt based on the antihypertensive effect.

4.5. Drugs interactions

This drug is mainly metabolized from cytochrome P450 3A4 (CYP3A4).

i.Contraindication along with the usage (Must not be used at the same time):

Drug Name	**Clinical Symptom/ Appropriate measures**	**Mechanism/Risk factor**
Azole antifungal drug Itraconazole, Miconazole etc.	It is reported that AUC of this drug will increase 28 times when this drug is simultaneously used with Itraconazole.	These drugs inhibit CYP3A4 and it is thought that there shall be a decrease in the clearance of this drug.
HIV Protease inhibitor (Ritonavir, Saquinavir, Indinavir etc.	There is a possibility of increased effect of this drug due to simultaneous usage.	

ii.Precautions at the time of simultaneous usage (Must be cautious while using simultaneously)

Drug name	**Clinical Symptom/ Appropriate measures**	**Mechanism/ Risk factor**
Other depressor drug	There is a possibility of excess low blood pressure. If it is required to reduce the dosage of this drug o other depressor drug.	There will be augmentation in the pharmacological effect due to the simultaneous usage of depressor drug whose working mechanism is different
Digoxin	It is reported that C_{max} and AUC of digoxin increases up to 1.5 and 1.3 times respectively due to simultaneous usage. If it is required to reduce the dosage of digoxin.	It is thought that it inhibits the renal excretion (tubular secretion) and non renal excretion of digoxin.
Cimentidine Imatinib mesylate Delavirdine mesylate Macrolide antibiotic Erythromycin Clarithromycin etc	There will be augmentation in the effect due to the simultaneous usage of this drug. If required, reduce the dosage of this drug or suspend the intake of these drugs.	These drugs inhibit CYP3A4 and it is thought that there shall be a decrease in the clearance of this drug.
Simvastatin	It is reported that AUC of Simuvastatin increases to 2.0 times due to simultaneous	It is thought that there shall be a decrease in the clearance of these drugs since these drugs

Drug name	Clinical Symptom/ Appropriate measures	Mechanism/ Risk factor
	usage. If required, suspend the intake of this drug or Simuvastatin.	inhibit competitively with CYP3A4. Especially, patients who are having a kidney function failure must be cautious.
Cyclosporine	There will be augmentation in the effect due to the simultaneous usage of this drug. If required, reduce the dosage of this drug or these medicines.	It is thought that there shall be a decrease in the clearance of these drugs since these drugs inhibit competitively with CYP3A4.
Benzodiazepine drug, Diazepam Midazolam Triazolam etc. orally active progestin / estrogenic hormone Oral contraceptive etc		
Tandospirone citrate	There will be augmentation in the effect due to the simultaneous usage of this drug. If required, reduce the intake of this drug or suspend the intake of Tandospirone citrate.	Blood pressure lowering effect of serotonin receptor mediated central nervous system can augment the pressure reduction effect.
Rifampicin Phenytoin Phenobarbital	There will be decrease in the effect due to the simultaneous usage of this drug.	It is thought that the clearance of this drug can increase due to the metabolizing enzyme inducing effect of these drugs.
Grape fruit juice	It is reported that there will be an increase in the blood concentration level while using this drug. Since there is a possibility of augmentation of pressure reducing effect, be cautious not to drink grape fruit juice while the patient is under medication of this drug.	The ingredients contained in grape fruit juice is CYP3A4 and this inhibit the metabolism of this drug and it is thought that this may deteriorate the clearence .

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

This drug must not be used by pregnant women or a woman who has the possibility to conceive.

Lactation

It is preferable to avoid the usage of this drug towards women who is under lactation, but lactation must be stopped in case of use of this drug in unavoidable situations.

Paediatric Patients

Safety towards baby with low birth weight, new born baby, lactating baby, infant or small child is not yet established (No experience over usage).

Geriatric Patients

When this drug is used by the aged individual, start the intake of this drug from 8mg or further lower quantity and it is preferable to cautiously intake while conducting the observations simultaneously over a period of time. [In general, for old aged individuals, excess pressure reduction is not preferable (More possibility of occurrence of cerebral infarction)].

4.7. Effects on ability to drive and use machines

Giddy feeling can be felt based on the antihypertensive effect of this medicine. Vehicle drivers and machine users should be informed of the risk related to using this medicine.

4.8. Undesirable effects

In a reported study, around 1,103 cases were investigated and out of these, 159 cases (14.4%) had reported side effects (certain objective symptom and abnormality shown in clinical examination value). Further, side effects seen in old aged individual who were more than 65 years old were 48 cases out of total 383 cases (12.5%).

**In total 5,169 cases were examined for its use result and out of which only 182 cases (3.5%) had reported side effects (including abnormality shown in clinical examination value).

i. Serious side effects

Liver function failure, Jaundice: Since there were cases which showed liver function failure, jaundice due to increase of AST (GOT), ALT (GPT), ´Y-GTP, please conduct enough observation and in case when the abnormality is recognized, stop the intake and must take appropriate measures.

Atrioventricular block, Sinus arrest, Bradycardia: Since there were cases where atrioventricular block, sinus arrest and bradycardia were shown, in case when dizziness, wobbling is recognized, stop the intake and must take appropriate measures.

ii. Other side effects

Since there were cases where the below mentioned side effects were seen, in case when the abnormality is recognized, upon necessity must take appropriate measures such as stopping the intake of the drug.

	Less than 0.1 to 1.0%	**Less than 0.1%**	**Frequency not clear** note1
Hypersensitivity note2	Rash	Itching	Swelling of blood vessel
Psychoneurotic system	Headache/heavy headed feeling, wobbling, dizziness, light headedness.	Drowsiness	
Digestive organ	Gastric distress, Nausea	Constipation, abdominal pains, diarrhoea	Enlarged gums, mouth ulcer
Circulatory organ	Palpitation, sensation of warmth, skin		

	flushing on face portion		
Blood		Drastic increase in eosinophil	
Liver	Increase in ALT, increase in AST, LDH increase, liver function abnormality, ALP increase.	Increase in total bilirubin	
Urinary organs	Increase in BUN	Increase in creatinine, increase in urie hyaline cast, frequent urination	
Others	Increase in urinary acid, increase in overall cholesterol, increase in CK(CPK), increase in potassium, fatigue, abnormal sensation (Light headedness, bad mood etc)	Reduction in potassium, swelling, numbness	Milky fluid in the abdomen[note3]

Note1: Frequency is not clear since these are the side effects which are reported in spontaneous report.
Note2: Must stop the intake. The solar photosensitivity symptom is reported for frequent medication.
Note3: It can easily occur in patients with hypoalbuminemia.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

There is no information on over dosage with Azelnidipine in humans. Over dosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional over dosage of Azelnidipine is limited. If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. If hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids.

5. Pharmacological properties

5.1. Mechanism of Action

Pharmacotherapeutic group: Dihydropyridine Ca antagonist

This drug represents lowering of the blood pressure by expanding the blood vessels based on L type and T type Ca channel antagonizing effect.

5.2. Pharmacodynamic properties

This medicine binds to membrane voltage-dependent L-type and T type calcium channels, reducing the influx of calcium into the cell, thereby relaxing the smooth muscle of peripheral vascular or coronary. In comparison with (diltiazem and verapamil) non-dihydropyridine calcium antagonist, vascular selectivity is high, inhibitory effect on heart rate and force of cardiac contraction is weak. Further, it should be noted that this medicine is characterized by the persistence of the action.

In a reported double blind comparison study, 8mg – 16mg 1 time per day for a period of 12 weeks continuously through double blind technique towards 208 patients who were showing minor to moderate symptoms of essential high blood pressure, the pressure reduction rate was observed to be 72.6% (it was 83.4% in case of excluding inability to determine).

Reportedly, in another double blind comparison study, the test which was targeted for patients who were showing minor to moderate symptoms of essential high blood pressure, this drug was given around 8 to 16mg for 756 cases and the pressure reducing rate was 73.7% (including inability to determine). In addition, clinical experiment result towards target patients who show different types of high pressure symptoms was as follows.

Name of Disorder	**Pressure Reduction Rate (Reduced Cases[#1]/Evaluated Cases)**	
Serious High Blood Pressure Symptoms	86.7%(26/30)	92.9%(26/28)
Blood Pressure Symptoms along with renal disorder	69.0%(20/29)	74.1%(20/27)

1.Declination: While meeting contraction phase blood pressure (More than - 20mmHg) and expansion phase blood pressure (more than -10mmHg), While meeting average blood pressure (more than -13mmHg), or even in case of declining trend#2), when the pressure has dropped below 150/90mmHg (However, it can be less than 140/85mmHg for patients who have been admitted)

2.Declining trend: While meeting contraction phase blood pressure (More than 10mmHg) and expansion phase blood pressure (more than -5mmHg), or while meeting the average blood pressure (more than -7mmHg).

3.Long term intake experiment

As per the reported data, the usage of this drug was examined when taken singularly and when taken along with other pressure reducing drugs other than calcium antagonistic drug as a single dose per day for a period of 52 weeks towards the patients who were showing minor to moderate symptoms of essential high blood pressure. The result shown was a stabilized pressure reducing effect

Method of intake	**Pressure reduction rate(Reduced Cases/ Evaluated Cases)**	
	Including "Inability to determine"	**Excluding "Inability to determine"**
Sole Therapy	87.4% (83/95)	91.2% (83/91)

Combined therapy with depressor drug other than calcium antagonist	76.7% (132/172)	85.2% (132/155)

5.3. Pharmacokinetic properties

Absorption

When the usage of Azelnidipine 8mg tablets 1 time per day for a period of 7 days continuously towards 6 male healthy adult individuals was examined, it took around 2 to 3 hours of time to reach the maximum blood plasma concentration and half-life period was around 19 to 23 hours. After 24 hours of the intake of the drug, the blood plasma concentration level was showing an approximately fixed value from day 2 and reached steady state immediately. Cmax and AUC0-∞ ware compared to the usage in empty stomach and usage after having food and were 38% and 69% respectively.

When the usage of Azelnidipine 8mg tablet as a single dose orally after breakfast towards 6 patients who are having mild/moderate symptoms of high blood pressure was examined, the time to reach the maximum blood plasma concentration was 3.7 hours, Cmax was 19.4ng/mL, half-life period (compatibility) was 6.1 hours and AUC0-24 was 66.5ng·hr/mL. It was thought that the blood plasma concentration was at the level similar to that of healthy individual.

Metabolism

The primary metabolic site is small intestine and liver and dihydropyridine ring is oxidized through CYP3A48.

Excretion

In the reported data of foreign individuals, when 4 healthy male individuals were examined for the usage of 14C-azelnidipine 4mg as a single dose orally, the total administered activity excretion rate in urine and excrement till 7 days after the intake of the drug was 26% and 63% respectively.

Liver Function Failure Patients

In the reported data of foreign individuals, when 8 healthy individuals and 8 patients who are having minor to moderate liver function failure were given a single dosage of Azelnidipine 8mg tablets orally, it showed almost similar blood plasma concentration shift.

Patients who are having High Blood Pressure along with Reduced Renal Function

When the usage of Azelnidipine 8mg tablet 1 time per day orally after breakfast for a period of 7 days continuously towards 6 patients (Serum creatinine 1.5 to 5.3mg/dL) who were having high blood pressure along with reduced renal function was examined, maximum blood plasma concentration on the 1st day of usage and 7th day of usage was 8.6ng/ml and 17.1ng/ml respectively, AUC0-24 was 67.3ng·hr/mL and 154.5 ng·hr/mL respectively and showed predominantly high values on 7th day but the blood plasma concentration after 24 hours after the intake showed almost a constant value after 6th day and then reached a steady state.

Old Aged Individuals

When the usage of Azelnidipine 8mg tablet 1 time per day orally after breakfast for a period of 7 days continuously towards 5 old aged (65 to 84 years) patients who are having high blood pressure symptoms was examined, the time to reach a maximum blood plasma concentration on the 1st day of usage and 7th day of usage was 4.4 hours and 3.3 hours respectively, half-life period was 6.4 hours and 8.6 hours respectively, AUC0-24 was 107.0ng·hr/mL and 242.8 ng·hr/mL respectively and predominantly high value was shown for maximum blood plasma concentration, half-life period and AUC0-24 on the 7th day but the blood plasma concentration

after 24 hours after the intake showed almost a constant value till 7th day and reached a steady state.

6. Nonclinical properties

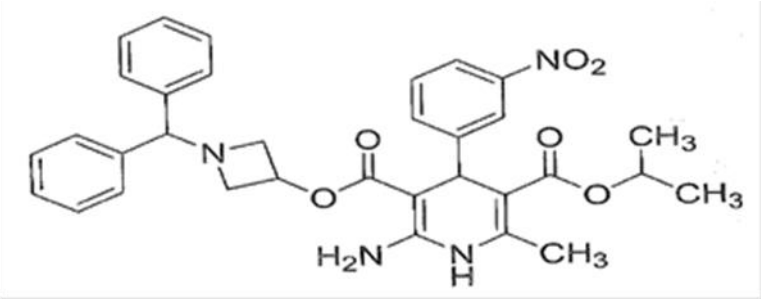
6.1. Animal Toxicology or Pharmacology

In experimentation with animals (rat), the drug was used before pregnancy to initial period, increase in embryonic death rate before implantation and after implantation, reduced body weight of the born child and extension in the pregnancy period and the delivery period are recognized. Further, extension in the pregnancy period and delivery period was seen while using this drug in the last term of pregnancy.

In experimentation with animals (rat), it is reported that it can be migrated during lactation.

7. Description

Azelnidipine is 3-O-(1-benzhydrylazetidin-3-yl) 5-O-propan-2-yl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. The empirical formula is $C_{33}H_{34}N_4O_6$ and its molecular weight is 582.6 g/mol. The chemical structure of Azelnidipine is:



UNIAZ 8 & 16 is Light yellow coloured, round, flat, uncoated tablet, scored on one side The excipients used are Lactose, Starch, Crospovidone, Polysorbate 80, Isopropyl alcohol, Colloidal silicon dioxide, Magnesium stearate, Low substituted Hydroxy propyl methyl cellulose.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

UNIAZ 8 & 16 is packed in Blister Pack of 10 Tablets

8.4. Storage and handing instructions

Store protected from ligt and moisture at a temperature not exceeding 25°C .

Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant

- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

M/s. Synokem pharmaceuticals Ltd.
Plot No. 56-57 Sector-6A,
I.I.E. (SIDCUL) , Ranipur (Bhel),
Haridwar- 249403 Uttrakhand

11. Details of permission or licence number with date

Mfg Lic No-27/UA/2018 issued on 17.07.2020.

12. Date of revision

AUG 2025

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/UNIAZ 8 mg, 16 mg/AUG-25/02/PI