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

UNIAZ CH

1. Generic Name

Azelnidipine and Chlorthalidone Tablets

2. Qualitative and quantitative composition

UNIAZ CH 8/6.25
Each uncoated tablet contains :
Azelnidipine I.P……..8 mg
Chlorthalidone I.P. ……6.25 mg
Excipients…… q.s.
The excipients used are Mannitol, Starch, Hydroxy propyl cellulose, Talcum, Crospovidone, Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate.

UNIAZ CH 8/12.5
Each uncoated tablet contains :
Azelnidipine I.P……..8 mg
Chlorthalidone I.P. …….12.5 mg
Excipients…… q.s.
The excipients used are Mannitol, Starch, Hydroxy propyl cellulose, Talcum, Crospovidone, Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate.

3. Dosage form and strength

Dosage form: Uncoated tablets

Strength: Azelnidipine 8 mg/ Chlorthalidone 6.25 mg and Azelnidipine 8 mg/ Chlorthalidone 12.5 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of essential hypertension.

4.2 Posology and method of administration

Dosage: As directed by the Physician

Method of administration:
UNIAZ CH tablets should be swallowed whole with a glass of water.
UNIAZ CH tablets may be administered with or without food.

4.3 Contraindications

UNIAZ CH should not be administered in the following patients:

- Women who may possibly be pregnant or are pregnant.
- Patients with a history of hypersensitivity to any component of this drug or other

sulphonamide derivatives.

- If combined with azole antifungals, (Itraconazole, Miconazole, etc.), HIV protease inhibitors (Ritonavir, Saquinavir, Indinavir, etc.) (See section "Drug interaction").
- Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia (history of gout or uric acid calculi), hypertension during pregnancy, untreated Addison's disease and concomitant lithium therapy.
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Azelnidipine

Must be used with caution in:

- 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.

Chlorthalidone

*Warnings***:**

Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis.
Chlorthalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

<u>Choroidal effusion, acute myopia and secondary angle-closure glaucoma</u>:
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible.

Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Precautions:

Electrolytes*:*

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hyperglycaemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by Chlorthalidone is dose dependent and varies in extent from one subject to another. With 25 to 50mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l. Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients. If necessary, Chlorthalidone may be combined with oral potassium supplements or a potassium sparing diuretic (eg triamterene).

If hypokalaemia is accompanied by clinical signs (eg muscular weakness, paresis and ECG alteration), Chlorthalidone should be discontinued.

Combined treatment consisting of Chlorthalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (eg nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, Chlorthalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlorthalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment. As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlorthalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlorthalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).
As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

4.5 Drugs interactions

Azelnidipine

This drug is mainly metabolized from cytochrome P4503A4 (CYP3A4).

- 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.	

- 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 or 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	It is thought that it inhibits the renal excretion (tubular secretion) and non-renal excretion of digoxin.

	required to reduce the dosage of digoxin.	
Cimetidine 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 usage. If required, suspend the intake of this drug or Simuvastatin.	It is thought that there shall be a decrease in the clearance of these drugs since these drugs inhibit competitively with CYP3A4. Especially, patients who are having a kidney function failure must be cautious.
Cyclosporine Benzodiazepine drug, Diazepam, Midazolam, Triazolam etc. orally-active progestin / estrogenic hormone Oral contraceptive 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 these medicines.	It is thought that there shall be a decrease in the clearance of these drugs since these drugs inhibit competitively with CYP3A4.
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	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 clearance.

	fruit juice while the patient is under medication of this drug.	

Chlorthalidone

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis induced cardiac arrhythmias.

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of Chlorthalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (eg atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach emptying rate.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as cholestyramine. A decrease in the pharmacological effect may be expected.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

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

Azelnidipine

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. [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.

Chlorthalidone
Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.
Chlorthalidone passes into the breast milk; mothers taking Chlorthalidone should refrain from breast-feeding their infants.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Azelnidipine

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).

<u>Serious side effects</u>

- 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.

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**[1]
Hypersensitivity[2]	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 (GPT), Increase in AST (GOT), LDH increase, Liver function abnormality, ALP increase	Increase in total bilirubin	
Urinary organs	Increase in BUN	Increase in creatinine, Increase in urine 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[3]

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

Chlorthalidone
Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%; uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:
Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.
Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.
Uncommon: gout.
Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.
Very rare: hypochloraemic alkalosis.

Skin:
Common: urticaria and other forms of skin rash.
Rare: photosensitisation.

Liver:
Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:
Common: postural hypotension.
Rare: cardiac arrhythmias.

Central nervous system:
Common: Dizziness.
Rare: paraesthesia, headache.

Gastro-intestinal tract:
Common: loss of appetite and minor gastrointestinal distress.
Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.

Very rare: pancreatitis.

Blood:
Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects:
Common: impotence
Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Azelnidipine

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.

Chlorthalidone
Signs and symptoms: In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment: There is no specific antidote to Chlorthalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

5. Pharmacological properties

5.1 Mechanism of Action

Azelnidipine

Pharmacotherapeutic group: Dihydropyridine Calcium 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 (inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls).

Chlorthalidone
Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action. Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the Na^+Cl^- cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+

and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

5.2 Pharmacodynamic properties

Azelnidipine

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)**	
	Including "Inability to determine"	**Excluding "Inability to determine"**
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 antagonists	76.7% (132/172)	85.2% (132/155)

Chlorthalidone

In persons with normal renal function, diuresis is induced after the administration of 12.5mg Chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, chlorthalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Chlorthalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlorthalidone reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensive potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

In renal diabetes insipidus, Chlorthalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

5.3 Pharmacokinetic properties

Azelnidipine

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. C_{max} and $AUC_{0-\infty}$ 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, C_{max} was 19.4ng/mL, half-life period (compatibility) was 6.1 hours and AUC_{0-24} 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 1^{st} day of usage and 7^{th} day of usage was 8.6ng/ml and 17.1ng/ml respectively, AUC_{0-24} was 67.3ng·hr/mL and 154.5 ng·hr/mL respectively and showed predominantly high values on 7^{th} 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 1^{st} day of usage and 7^{th} day of usage was 4.4 hours and 3.3 hours respectively, half-life period was 6.4 hours and 8.6 hours respectively, AUC_{0-24} 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 AUC_{0-24} on the 7^{th} 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.

Chlorthalidone

Absorption and plasma concentration

The bioavailability of an oral dose of 50mg Chlorthalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, Cmax values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, are reached after 1 to 2 weeks.

Distribution

In blood, only a small fraction of chlorthalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlorthalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlorthalidone is about 76% and the major binding protein is albumin. Chlorthalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlorthalidone daily before and after delivery, chlorthalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlorthalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.

Elimination

Chlorthalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlorthalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special patient groups

Renal dysfunction does not alter the pharmacokinetics of chlorthalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

No dosage adjustment is needed in patients with impaired renal function.

In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Azelnidipine

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.

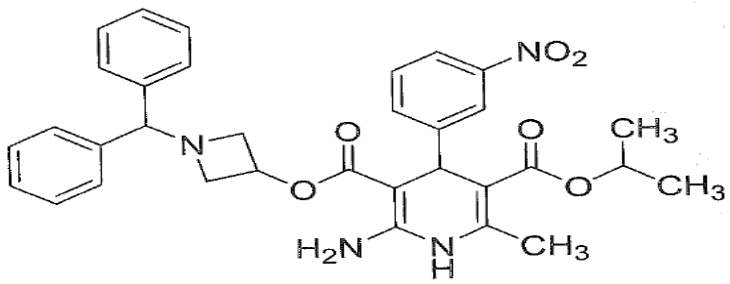
Chlorthalidone

There are no pre-clinical data of relevance to the prescriber.

7. Description

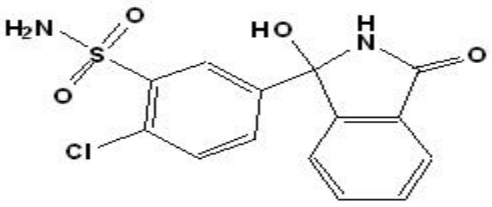
Azelnidipine

Azelnidipine is 3-(1-Benzhydrylazetidin-3-yl) 5-isopropyl 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)pyridine-3 ,5-dicarboxylate. The empirical formula is $C_{33}H_{34}N_4O_6$ and its molecular weight is 582.7 g/mol. The chemical structure of Azelnidipine is:



Chlorthalidone

Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



Chlorthalidone is a white to yellowish-white, crystalline powder which is soluble in methanol; slightly soluble in ethanol (95%); practically insoluble in water, in ether and in chloroform.

UNIAZ CH 8/6.25

Azelnidipine and Chlorthalidone Tablets are pale yellow coloured, round, flat, uncoated tablets, scored on one side. The excipients used are Mannitol, Starch, Hydroxy propyl cellulose, Talcum, Crospovidone, Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate.

UNIAZ CH 8/12.5

Azelnidipine and Chlorthalidone Tablets are light yellow coloured, round, flat, uncoated tablets, scored on one side. The excipients used are Mannitol, Starch, Hydroxy propyl cellulose, Talcum, Crospovidone, Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

UNIAZ CH is packed in blister pack of 10 tablets.

8.4 Storage and handing instructions

Store below 30°C & protect from light and moisture.
Keep all medicines out of reach of children

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What UNIAZ CH is and what it is used for

UNIAZ CH contains the active substance Azelnidipine and Chlorthalidone. Azelnidipine is Dihydropyridine Ca^{2+} channel antagonist and Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic.

UNIAZ CH is used for the treatment of essential hypertension.

9.2 What you need to know before you take UNIAZ CH

Do not take UNIAZ CH:

– if you are allergic to Azelnidipine & Chlorthalidone, or to any of the other ingredients of this medicine.

– If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

– If you are using Azole antifungal drugs (Itraconazole, Miconazole etc) and HIV Protease inhibitors (Ritonavir, Saquinavir, Indinavir etc)

– If you are a Pregnant women or women who has a possibility to become conceive.

If any of the above applies to you, tell your doctor or pharmacist before taking UNIAZ CH.

Warnings and precautions

Talk to your doctor before taking UNIAZ CH if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes

Talk to your doctor before taking UNIAZ CH:

- If you are taking any of the following medicines used to treat high blood pressure: an ACE-inhibitor (for example enalapril, lisinopril, and Ramipril).

- If you are taking digoxin, Cimetidine, Imatinib mesylate, Grape fruit juice, Rifampicin and Phenytoin

- If you are taking Lithium containing medicines to treat some types of depression.
- If you are taking medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor antagonists, NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressive (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.

Children

The use of UNIAZ CH is not recommended in children and adolescents.

Other medicines and UNIAZ CH

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

UNIAZ CH with food, drink and alcohol

Caution is advised: Low blood pressure may be aggravated by alcohol, barbiturates, narcotics or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking UNIAZ CH.

Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking UNIAZ CH before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of UNIAZ CH. UNIAZ CH is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. UNIAZ CH is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Some people feel dizzy, giddy feeling or tired when taking UNIAZ CH. If you feel dizzy or tired, do not drive or operate machinery.

9.3 How to take UNIAZ CH

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet a day.

Method of administration: The tablet must be taken orally, swallowed whole with liquid and may be taken with or without food.

Special dosage instructions for specific populations:
Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose is recommended in these patients.

Hepatic impairment

UNIAZ CH is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment, the posology should be as directed by Physician.

Elderly patients aged 65 years and above

No dose adjustment is necessary for elderly patients.

If you take more UNIAZ CH than you should

Tell your doctor or pharmacist if you have taken more than the recommended dose. If possible take your medicine and this leaflet with you.

If you forget to take UNIAZ CH

Do not take a double dose to make up for the forgotten dose. Take your next, normal dose, the next day, at your usual time.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

9.4 Possible side effects

Azelnidipine

Serious side effects

- Liver function failure and Jaundice
- Cardiac Arrest, Sinus Block and slowed heart rate (Bradycardia)

The following **very common** and **common** side effect has been reported. If this causes you problems, you should contact your doctor.

- **Very Common:** Rash, Headache/Heavy headed feeling, wobbling, dizziness, light-headedness, Gastric distress, Nausea, Palpitation, Sensation of warmth, Skin flushing on face portion, Increase in ALT (GPT), Increase in AST (GOT), LDH increase, Liver function abnormality, ALP increase, Increase in Blood Urea Nitrogen (BUN), Increase in urinary acid, increase in overall cholesterol, Increase in CK (CPK), Increase in potassium, Fatigue, abnormal sensation (Light headedness, bad mood etc.).
- **Common:** Itching, Drowsiness, Constipation, abdominal pains, Diarrhoea, Drastic increase in eosinophil, Increase in total bilirubin, Increase in creatinine, Increase in urine hyaline cast, Frequent urination, Reduction in potassium, Swelling, Numbness.
- Following events can also be experienced while being on Azelnidipine: Swelling of blood vessel, Enlarged gums, Mouth ulcer, Milky fluid in the abdomen

Chlorthalidone

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%; uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.

Uncommon: gout.

Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.

Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria and other forms of skin rash.

Rare: photosensitisation.

Liver:

Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:

Common: postural hypotension.

Rare: cardiac arrhythmias.

Central nervous system:

Common: Dizziness.

Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite and minor gastrointestinal distress.

Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.

Very rare: pancreatitis.

Blood:

Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Other effects:

Common: impotence

Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store UNIAZ CH

Store below 30°C & protect from light and moisture.

9.6 Contents of the pack and other information

What **UNIAZ CH** contains

The active substances **UNIAZ CH** is Azelnidipine & Chlorthalidone.

The excipients used are Mannitol, Starch, Hydroxy propyl cellulose, Talcum, Crospovidone, Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate.

10. Details of manufacturer

Manufactured in India by:

Synokem Pharmaceuticals Ltd.
Plot No. 56-57, Sector-6A, I.I.E. (SIDCUL), Ranipur (BHEL), Haridwar – 249403 (Uttarakhand).

11. Details of permission or licence number with date

Mfg Lic No. 27/UA/2018 issued on 06.03.2021

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/UNIAZ CH 8,6.25mg and 8,12.5mg/MAR-21/01/PI