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

UNIAZ-T

1. Generic Name

Azelnidipine and Telmisartan Tablets

2. Qualitative and quantitative composition

Each film coated bi-layered tablet contains:
Azelnidipine IP……. 8 mg / 8 mg
Telmisartan IP……40 mg / 80 mg
Colours: Ponceau 4R Lake (In Telmisartan layer)

The excipients used are Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Starch Primellose, Primojel, Colloidal Silicone Dioxide, Colour Ponceau 4R Lake, Mannitol, Hydroxy Propyl Cellulose, Crospovidone, Microcrystalline Cellulose, Hydroxy propyl Methyl Cellulose, Methylene Dichloride, Lactose.

3. Dosage form and strength

Dosage form: Film coated Tablets

Strength: Azelnidipine 8 mg/Telmisartan 40 mg and Azelnidipine 8 mg/Telmisartan 80 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of patients with Stage II hypertension

4.2 Posology and method of administration

Posology

Adults

One tablet once a day or as directed by physician.

Elderly

No dose adjustment is necessary for elderly patients.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

UNIAZ-T is contraindicated in patients with severe hepatic impairment.

In patients with mild to moderate hepatic impairment, dose of telmisartan should not exceed 40 mg once daily.

Paediatric population

The safety and efficacy of UNIAZ-T in children and adolescents aged below 18 years have not been established.

Method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Pregnant women or women who has a possibility to conceive.

4.4 Special warnings and precautions for use

Telmisartan

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment

Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation

When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyper azotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.
In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressive (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Close monitoring of serum potassium in at risk patients is recommended.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

Azelnidipine

Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of Azelnidipine, particularly in patients with severe obstructive coronary artery disease.

Beta-Blocker Withdrawal

Azelnidipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure

Because Azelnidipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients.

4.5 Drugs interactions

Telmisartan

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressive (cyclosporin or tacrolimus), and trimethoprim.

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed. Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution.

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination

should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and Ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.
To be taken into account with concomitant use.

Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensive including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

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 required to reduce the dosage of digoxin.	It is thought that it inhibits the renal excretion (tubular secretion) and non-renal excretion 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	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.	
Benzodiazepine drug, Diazepam, Midazolam, Triazolam etc. orally-active progestin / estrogenic hormone Oral contraceptive etc		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 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 clearance.

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

Pregnancy

-The use of Uniaz T is not recommended during the first trimester of pregnancy. -The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.
Warning: Fetal Toxicity When pregnancy is detected, discontinue the product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Studies in animals have shown reproductive toxicity.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia).

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

Breast-feeding

Because no information is available regarding the use of Uniaz T during breast-feeding, it is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

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 at the lowest dose and it is preferable to monitor blood pressure 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

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

Telmisartan

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4 % vs 43.9 %) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations	
Uncommon:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis
Rare:	Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia
Immune system disorders	
Rare:	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	
Uncommon:	Hyperkalaemia
Rare:	Hypoglycaemia (in diabetic patients)
Psychiatric disorders	
Uncommon:	Insomnia, depression
Rare:	Anxiety
Nervous system disorders	
Uncommon:	Syncope
Rare:	Somnolence
Eye disorders	
Rare:	Visual disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Bradycardia

Rare:	Tachycardia
Vascular disorders	
Uncommon:	Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough
Very rare:	Interstitial lung disease[4]
Gastrointestinal disorders	
Uncommon: Rare:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting Dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders	
Rare:	Hepatic function abnormal/liver disorder[3]
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, hyperhidrosis, rash
Rare:	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Musculoskeletal and connective tissue disorders	
Uncommon:	Back pain (e.g. sciatica), muscle spasms, myalgia
Rare:	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	
Uncommon:	Renal impairment including acute renal failure
General disorders and administration site conditions	
Uncommon:	Chest pain, asthenia (weakness)
Common:	Fatigue, asthenia
Very common:	Oedema

Rare:	Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

[1, 2, 3,4]: for further descriptions, please see sub-section *"Description of selected adverse reactions".*

Description of selected adverse reactions

Sepsis

In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

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).

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.

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.

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

Telmisartan

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness.

There is limited information available with regard to overdose in humans.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Management

Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

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

5. Pharmacological properties

5.1 Mechanism of Action

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin in system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by Telmisartan. Plasma aldosterone levels are decreased by Telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.
In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

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).

5.2 Pharmacodynamic properties

Telmisartan

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

<u>Clinical efficacy and safety</u>

<u>Treatment of essential hypertension</u>

In reported study after the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.
The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in reported placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in reported clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in reported clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.
In reported study Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen for Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

The reported two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. For more detailed information, see above under the heading “Cardiovascular prevention”. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early

because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

The safety and efficacy of UNIAZ-T in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.

An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.

These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

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)

5.3 Pharmacokinetic properties

Telmisartan

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Paediatric population

The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for Cmax.

Gender

Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

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 7^{th} day and reached a steady state.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamic (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offspring's such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

Azelnidipine

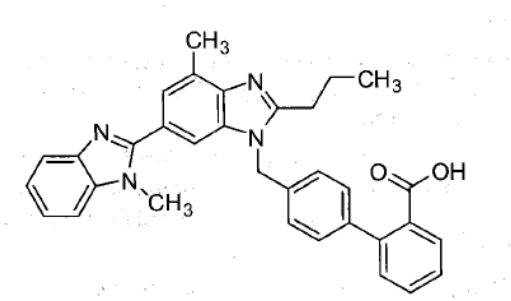
In experimentation with animals (rat), the drug was used before pregnancy to initial period, increase in embryonic death rate before implantation and after implantation, reduced body weight of the born child and extension in the pregnancy period and the delivery period are recognized. Further, extension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

7. Description

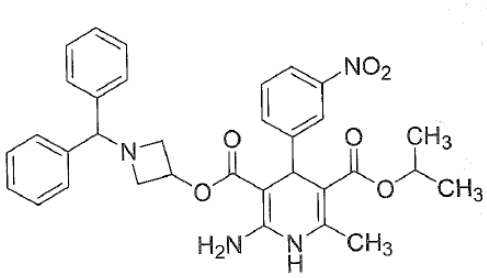
Telmisartan

Telmisartan is 4'-{[4-methyl-6-(1-methyl-lH-benzimidazol-2-yl)-2-propyl-lH-benzimidazol-1-yl]methyl}-2-biphenyl- carboxylic acid. It is a white off white crystalline powder. Its chemical formula is $C_{33}H_{30}N_4O_2$ & the molecular weight is 514.6 g/mol and the chemical structure is:



Azelnidipine

Azelnidipine is 3-(1-Benzhydrylazetidin-3-yl) 5-isopropyl 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.It is a light yellow to yellow crystalline powder. Its chemical formula is $C_{33}H_{34}N_4O_6$ the molecular weight is 582.7 g/mol and the chemical structure is:



Azelnidipine and Telmisartan Tablets (8mg + 40mg) / (8mg + 80mg) is one side light yellow coloured and other side light pink coloured, round, biconvex, plain on both sides, bi-layered, film coated tablets. The excipients used are Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Starch Primellose, Primojel, Colloidal Silicone Dioxide, Colour Ponceau 4R Lake, Mannitol, Hydroxy Propyl Cellulose, Crospovidone, Microcrystalline Cellulose, Hydroxy propyl Methyl Cellulose, Methylene Dichloride, Lactose.

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-T is available Alu-Alu blister pack of 10 tablets.

8.4 Storage and handing instructions

Store in cool, dark and dry place.
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-T is and what it is used for

UNIAZ-T contains the active substance Azelnidipine and Telmisartan. Telmisartan is angiotensin II receptor (type AT1) antagonist and Azelnidipine is Dihydropyridine Ca^{2+} channel antagonist.

UNIAZ-T is used for the treatment of Stage II hypertension.

9.2 What you need to know before you take UNIAZ-T

Do not take UNIAZ-T:

– if you are allergic to Azelnidipine & Telmisartan, 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-T.

Warnings and precautions

Talk to your doctor before taking UNIAZ-T 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-T:

- 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-T is not recommended in children and adolescents.

Other medicines and UNIAZ-T

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

UNIAZ-T 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-T.

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-T before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of UNIAZ-T. UNIAZ-T 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-T 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-T. If you feel dizzy or tired, do not drive or operate machinery.

9.3 How to take UNIAZ-T

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 film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

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-T 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-T 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-T

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

Telmisartan

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms:
Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory Response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking

the medicine and see their doctor immediately. If these effects are not treated they could be fatal.

Possible side effects of Telmisartan

Common side effects (may affect up to 1 in 10 people):
Low blood pressure (hypotension).

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels, difficulty falling asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), slow heart rate (bradycardia), low blood pressure (hypotension) in users treated for high blood pressure, dizziness on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhoea, discomfort in the abdomen, bloating, vomiting, itching, increased sweating, drug rash, back pain, muscle cramps, muscle pain (myalgia), kidney impairment including acute kidney failure, pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people):
Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heart beat (tachycardia), dry mouth, upset stomach, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin and mucosa which can also lead to death (angioedema also with fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flulike- illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood.

Very rare side effects (may affect up to 1 in 10,000 people):
Progressive scarring of lung tissue (interstitial lung disease) **.

* The event may have happened by chance or could be related to a mechanism currently not known.

** Cases of progressive scarring of lung tissue have been reported during intake of telmisartan. However, it is not known whether telmisartan was the cause.

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

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-T

Store in cool, dark and dry place.

9.6 Contents of the pack and other information

What **UNIAZ-T** contains

The active substances **UNIAZ-T** is Azelnidipine & Telmisartan.

The excipients used are Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum, Magnesium Stearate, Sodium Starch Glycolate, Starch Primellose, Primojel, Colloidal Silicone Dioxide, Colour Ponceau 4R Lake, Mannitol, Hydroxy Propyl Cellulose, Crospovidone, Microcrystalline Cellulose, Hydroxy propyl Methyl Cellulose, Methylene Dichloride, Lactose.

10. Details of manufacturer

Manufactured in India by:

Synokem Pharmaceuticals Ltd.
Plot No. 35-36, Sector-6A, Integrated Industrial Estate (SIDCUL), Ranipur,
(BHEL), Haridwar-249403 (Uttarakhand).

11. Details of permission or licence number with date

Mfg Lic No. 27/UA/2018 issued on 24.08.2020

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/UNIAZ-T 8,40mg and 8,80mg/SEP-20/01/PI