To be sold by retail on the Prescription of R.M.P. only

AZOVAS® T40 AZOVAS® T80

℞ Azelnidipine and Telmisartan Tablets

WARNING: AVOID USE IN PREGNANCY

When pregnancy is detected, discontinue tablets as soon as possible.

Drugs that act directly on the renin-angiotensin system like Telmisartan can cause injury and even death to the developing foetus.

COMPOSITION

Azovas® T 40

Each film coated bilayered tablet contains:

Azelnidipine IP ..... 8 mg
Telmisartan IP ..... 40 mg

Colours: Ferric Oxide USPNF Yellow & Titanium Dioxide IP

COMPOSITION

Azovas® T 80

Each film coated bilayered tablet contains:

Azelnidipine IP ..... 8 mg
Telmisartan IP ..... 40 mg

Colours: Ferric Oxide USPNF Yellow & Titanium Dioxide IP

PHARMACEUTICAL FORM

Film Coated Bi-layered Tablet

THERAPEUTIC INDICATION

It is indicated for the treatment of stage II hypertension.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

The recommended adult dose is 1 tablet once daily or as directed by the Physician. Dosage must be individualized.

Special population:

Pediatric Use: Safety and effectiveness of the FDC of Azelnidipine/Telmisartan in pediatric patients have not been established.

Elderly: The FDC of Azelnidipine/Telmisartan should be administered carefully in elderly patients. When used in elderly, start the administration with low dose or even 8 mg of Azelnidipine, administer carefully. In the elderly, there is a possibility that the cerebral infarction occurs, due to excessive and undesirable hypotension in general.

Method of administration: For oral administration only.

The patients should be instructed to swallow the Azelnidipine/Telmisartan tablet whole with liquid and must not be chewed, split or crushed. To achieve the best possible

results, take your dose at the same time(s) each day.

CONTRAINDICATIONS

It is contraindicated in patients with a known hypersensitivity to any of the active substance(s) or any of other components of this product. Azelnidipine is contraindicated in the following patients:

- Women who may possibly be pregnant or are pregnant (See section "Use in special population").
- If combined with azole antifungals, (Itraconazole, Miconazole, etc.), HIV protease inhibitors (Ritonavir, Saquinavir, Indinavir, etc.) See section "Drug interaction". Telmisartan is contraindicated in the following patients:
- Second and third trimester of pregnancy.
- Biliary obstructive disorders.
- Severe hepatic impairment.
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warning: Avoid use in Pregnancy

When pregnancy is detected, discontinue Azelnidipine/Telmisartan tablets as soon as possible. Drugs that act directly on the renin-angiotensin system like Telmisartan can cause injury and even death to the developing foetus.

Azelnidipine

Careful administration (It should be administered with caution in the following patients):

- Patients with serious liver and kidney dysfunction. The drug is metabolized in the liver. Also in patients with severe renal dysfunction in general, there is a possibility that the renal function is reduced.
- Elderly (See section "Use in Special Population").

Important Precautions:

- When administration of calcium antagonists stopped abruptly, it have been reported that patients develop symptoms, which reduced gradually when with washout of the drug, it should be carefully monitored. Also, be careful not to stop the medication without a physician's supervision to the patient.
- Because with the administration of this drug there is a risk of excessive decrease of pressure in rare cases, make appropriate measures such as dose reduction or withdrawal from medication in such cases.
- Because it may cause dizziness based on the hypotensive effects, take precautions when working with dangerous operation of aerial work, automotive and machinery.
- Myocardial infarction, arrhythmia and heart failure (atrial fibrillation, etc.) have been reported during treatment with this drug, though causal relationship is not clear.
- It has been reported that dialysis effluent of CAPD (continuous ambulatory peritoneal dialysis) patients becomes clouded, it is important to note the differential diagnosis from peritonitis, etc.
- Do not drink grapefruit juice while you take this medicine because it may increase blood concentration of the medicine and cause an excessive hypotensive response.
- Patients should be closely monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. Hepatic function disorder, jaundice with elevations of AST (GOT), ALT (GPT), γ-GTP, and jaundice may occur.

If you miss a dose, take the missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. You should never take two doses at one time.

Do not stop taking this medicine unless the doctor instructs to do so.

Telmisartan

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, and diarrhoea or vomiting. Such conditions should be corrected before the 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. 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, hyperazotaemia, 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-an-giotensin 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.

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.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

DRUG INTERACTIONS

Azelnidipine

Azelnidipine is metabolized by hepatic cytochrome P450 (CYP) 3A4 and has no active metabolite product. It may interact with other drugs or compounds that are substrates for this enzyme.

Combination contraindicated:

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

Use with Caution:

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

Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, the 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, immunosuppressives (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.

Lithium: Reversible increases in the 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.

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.

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 antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic use): Reduction of the antihypertensive effect.

USE IN SPECIFIC POPULATIONS

Pregnancy

Azelnidipine 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].

The use of angiotensin II receptor antagonists 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.

There are no adequate data from the use of Telmisartan in pregnant women. 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 medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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's therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohy- dramnios, 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.

Nursing Mothers

Azelnidipine: 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].

Telmisartan: It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric use

Safety and effectiveness of the FDC of Azelnidipine/Telmisartan in pediatric patients have not been established. Azelnidipine: Never Use; Safety for low birth weight infants, newborns, infants and children has not been established.

Neonates with a history of in utero exposure to telmisartan: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Ex- change transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Of the total number of patients receiving telmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment of telmisartan is necessary for elderly patients.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of telmisartan 20 mg is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

Telmisartan is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment; the posology should not exceed telmisartan 40 mg once daily. Monitor carefully and up-titrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since the antihypertensive activity of Azelnidipine may induce dizziness and lightheaded (due to blood pressure dropping, or hypotension). So, the patients should be cautioned to pay much attention in engaging in potentially hazardous activities such as driving a car, work at heights or using machines while taking this medicine.

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

UNDESIRABLE EFFECTS

Azelnidipine

The most commonly reported adverse reactions include headache, dull headache, constipation, drowsiness, general malaise, lightheadedness, diarrhoea and epigastric pressure.

Clinically significant adverse reactions (incidence unknown):

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

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

Other side effects:

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

	Less than 0.1 - 1%	Less than 0.1%	Incidence unknown [Note1]
Hypersensitivity[2]	Rash	Itching	Angioedema
Neuropsychiatric	Headache, heaviness of the head, Lightheadedness, Dizziness	Drowsiness	
Digestive system	Stomach discomfort, nausea	Constipation, abdominal pain, diarrhea	Gingival hypertrophy, Stomatitis
Circulatory system	Palpitations, hot flashes, hot flushes		
Blood Related	Eosinophilia		
Hepatic	ALT (GPT) elevation, AST (GOT) rise, LDH rise, γ-GTP rise, Abnormal liver function, ALP rise	Total bilirubin Rise	
Urinary system	BUN increased	Creatinine rise, Increase urine, Frequent urination	
Others	Uric acid increased, Increased total cholesterol, CK (CPK) increased, Potassium increased, malaise, (Floating feeling, feeling abnormal sense of Defect etc.)	Potassium decreased, Edema, Numbness	Chylous ascites[3]

[1] Incidence unknown, because the side effects are observed in spontaneous reporting.

[2] Administration of this product should be discontinued. Further, photosensitivity has been reported in analogous drugs.

[3] It is easy to occur in patients with hypoalbuminemia.

Telmisartan

Clinical Trials Experience:

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Hypertension:

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are as follows: Upper respiratory tract infection, back pain, sinusitis, diarrhea and pharyngitis.

In addition to these adverse events (above), the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of patients treated with telmisartan and 6.1% of patients treated with placebo, in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients. The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets:

Autonomic Nervous System: impotence, increased sweating, flushing.

Body as a Whole: allergy, fever, leg pain, malaise.

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal echocardiography (ECG).

Central Nervous System: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders.

Metabolic: gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: arthritis, arthralgia, leg cramps.

Psychiatric: anxiety, depression, nervousness.

Resistance Mechanism: infection, fungal infection, abscess, otitis media.

Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis.

Skin: dermatitis, rash, eczema, pruritus.

Urinary: micturition frequency, cystitis.

Vascular: cerebrovascular disorder.

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings:

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy because of increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo.

No telmisartan-treated patients discontinued therapy because of abnormal hepatic function.

Post-marketing Experience:

The following adverse reactions have been identified during post-approval use of telmisartan. Because these reactions are reported voluntarily from a population of uncer- tain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan. The most frequent spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dys- function, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Reporting of suspected adverse reactions

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

OVERDOSE

Azelnidipine

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

As with any calcium channel blocker toxicity, bradycardia and hypotension may result from overdose. The treatment of patients with bradycardia and hypotension begins with supportive therapy and atropine; however, patients with severe toxicity do not have an adequate response and must be managed more aggressively.

Calcium plays an imperative role in myocardial contractility, automaticity and vascular tone. Administration of exogenous calcium is of benefit in cases of toxicity.

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Azelnidipine

Azelnidipine is a third generation; long-acting dihydropyridine (DHP) based calcium channel blocker (CCB). It is a vasodilator that induces a gradual decrease in blood pressure in hypertensive patients. Unlike other members of its drug class, azelnidipine does not induce reflex tachycardia due to vasodilation. This is likely due to the fact that it elicits a gradual fall in blood pressure. It also exhibits a prolonged hypotensive effect and has been shown to have a strong anti-arteriosclerotic action in vessels due to its high affinity for vascular tissue and antioxidative activity. Clinical studies have demonstrated that azelnidipine markedly reduced heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance.

Mechanism of action: Azelnidipine inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls. Ca2+ channels are classified into various categories, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels. The L-type Ca2+ channels 6. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased blood pressure.

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. 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 characterized 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 events. 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.

Pharmacokinetic Properties

Azelnidipine

Oral ingestion of azelnidipine demonstrates rapid and dose-dependent absorption. After multiple-dose of Azelnidipine 8 mg/day for 7 days, C_{max} and AUC 24 hr values were 14.7 ng/ml and 81.6 ng.hr/ml; Tmax on 7 days was 2.2 hrs. Steady-state plasma concentrations of Azelnidipine achieved after 2 days. As a result of a single oral dose of 8 mg Azelnidipine tablets after breakfast in six mild-moderate essential hypertension patients, time to reach peak plasma concentration was 3.7 hours, C_{max} 9.4 ng/ml, half-life (monophasic) 6.1 hours and AUC0-24 was 66.5ng • hr / ml. Plasma concentration was considered to levels similar to healthy adults. In vitro plasma protein binding rate of this drug is 90-91%, and non-specific binding is with lipoproteins mainly. In a Chinese study examining the pharmacokinetics of the drug, the volume of distribution was found to be 1749 +/- 964 7. Like most members of its class, azelnidipine primarily undergoes first-pass hepatic metabolism. Azelnidipine is metabolized by hepatic cytochrome P450 (CYP) 3A4 and has no active metabolite product. It may interact with other drugs or compounds that are substrates

for this enzyme. Azelnidipine is lipophilic and has a potent affinity for membranes of vascular smooth muscle cells. The main metabolic sites are liver and small intestine, dihydropyridine ring is oxidized by CYP3A4. In data from studies, it was found that after a single oral dose of 4 mg 14C-Azelnidipine to four healthy adult male, the total administered radioactivity excretion rate to the feces and urine up to 7 days after administration, was 26% in urine and the 63% in feces. Half-life of azelnidipine: 16 –28 hours.

Telmisartan

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 (AUC0-∞) 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. Telmisartan is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l. Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Telmisartan is characterized 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).

INCOMPATIBILTY

Not known.

STORAGE AND HANDLING INSTRUCTIONS

Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep out of reach of children.

PACKAGING INFORMATION

Blister of 2 Tablets & 10 Tablets

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
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Note: This prescribing information is applicable for India Market only.