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

UNIAZ BETA

1. Generic Name

Azelnidipine & Metoprolol Succinate (Sustained Release) Tablets (8+25 & 8+50, 16+25 & 16+50)

2. Qualitative and quantitative Composition:

UNIAZ BETA 8/25

Each Film Coated Bilayered Tablet Contains:

Azelnidipine I.P. ……..…8 mg

Metoprolol Succinate I.P.

Eq. to Metoprolol Tartrate……..25 mg

(as Sustained Release)

Colours: Ferric Oxide USPNF Yellow & Titanium Dioxide I.P.

The Excipients used are Microcrystalline Cellulose, Dibasic Calcium Phosphate , Colloidal Silicon Dioxide, Mannitol, Sodium Bicarbonate, Crosspovidon, Polysorbate, Isopropyl Alcohol, Methylene Dichloride, Hydroxy Propyl Cellulos, Sodium Bicarbonate, Magnesium Stearate, Xanthan Gum, Methocel K 100 M Premium Dow, Hydroxy Propyl Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Stearyl Fumarate, Akoat Purified Water.

UNIAZ BETA 8/50

Each Film Coated Bilayered Tablet Contains:

Azelnidipine I.P. ……..…8 mg

Metoprolol Succinate I.P.

Eq. to Metoprolol Tartrate…..……..50 mg

(as Sustained Release)

Colours: Ferric Oxide USPNF Red & Titanium Dioxide I.P.

The Excipients used are Microcrystalline Cellulose, Dibasic Calcium Phosphate , Colloidal Silicon Dioxide, Mannitol, Sodium Bicarbonate, Crosspovidon, Polysorbate, Isopropyl Alcohol, Methylene Dichloride, Hydroxy Propyl Cellulos, Sodium Bicarbonate, Magnesium Stearate, Xanthan Gum, Methocel K 100 M Premium Dow, Hydroxy Propyl Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Stearyl Fumarate, Akoat Purified Water.

UNIAZ BETA 16/25

Each Film Coated Bilayered Tablet Contains:

Azelnidipine I.P. ……..…...16 mg

Metoprolol Succinate I.P.

Eq. to Metoprolol Tartrate……25 mg

(as Sustained Release)

Colours: Sunset Yellow FCF & Titanium Dioxide I.P.

The Excipients used are Microcrystalline Cellulose, Dibasic Calcium Phosphate, Colloidal Silicon Dioxide, Mannitol, Sodium Bicarbonate, Crosspovidone, Polysorbate, Isopropyl Alcohol, Methylene Dichloride, Hydroxy Propyl Cellulose, Sodium Bicarbonate, Magnesium Stearate, Xanthan Gum, Methocel K 100 M Premium Dow, Hydroxy Propyl Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Stearyl Fumarate, Akoat, Purified Water.

UNIAZ BETA 16/50

Each Film Coated Bilayered Tablet Contains:

Azelnidipine I.P. ……...16 mg

Metoprolol Succinate I.P.

Eq. to Metoprolol Tartrate…..……..50 mg

(as Sustained Release)

Colours: Quinoline Yellow & Titanium Dioxide I.P.

The Excipients used are Microcrystalline Cellulose, Dibasic Calcium Phosphate, Colloidal Silicon Dioxide, Mannitol, Sodium Bicarbonate, Crosspovidone, Polysorbate, Isopropyl Alcohol, Methylene Dichloride, Hydroxy Propyl Cellulose, Sodium Bicarbonate, Magnesium Stearate, Xanthan Gum, Methocel K 100 M Premium Dow, Hydroxy Propyl Cellulose, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Stearyl Fumarate, Akoat, Purified Water

3. Dosage form and strength

Dosage form: Film Coated Bilayered Tablet

Strength: Azelnidipine & Metoprolol Succinate (8+25 & 8+50, 16+25 & 16+50) mg

4. Clinical particulars

4.1. Therapeutic indication

For the treatment in stage 2 Hypertension.

4.2. Posology and method of administration

Posology

The recommended dose is 1 tablet once daily or as directed by the physician.

Method of administration

For oral administration only.

4.3. Contraindications

Hypersensitivity to any of the active substance (s) or to any of the excipient of the formulation. Metoprolol is contraindicated in severe bradycardia, second- or third-degree heart block, cardiogenic shock, decompensated heart failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

4.4. Special warnings and precautions for use

Azelnidipine

With your blood pressure dropping, you may feel dizzy and lightheaded. Do not work at heights, drive a car or operate dangerous machinery while you take this medicine.

Do not drink grapefruit juice while you take this medicine because it may increase drug blood concentration and cause an excessive hypotensive response.

Hepatic function disorder, jaundice: Hepatic function disorder with elevations of AST (GOT), ALT (GPT), γ-GTP, and jaundice may occur.

Metoprolol

Abrupt Cessation of Therapy

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction has occurred. When discontinuing chronically administered Metoprolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate Metoprolol, and take appropriate measures for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing Metoprolol in patients treated only for hypertension.

Heart Failure

Worsening cardiac failure may occur during up-titration of Metoprolol. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of Metoprolol. It may be necessary to lower the dose of Metoprolol or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Metoprolol.

4.5. Drugs interactions

Azelnidipine

Reported drug interaction with azelnidipine are as given below:

2-HYDROXY-1,4-NAPHTHOQUINONE	The risk or severity of adverse effects can be increased when 2-HYDROXY-1, 4-NAPHTHOQUINONE is combined with Azelnidipine.
2-mercaptobenzothiazole	The risk or severity of adverse effects can be increased when 2-mercaptobenzothiazole is combined with Azelnidipine.
Alfuzosin	Alfuzosin may increase the hypotensive activities of Azelnidipe.
Amobarbital	The metabolism of Azelnidipine can be increased when combined with Amobarbital.
Amorolfine	The risk or severity of adverse effects can be increased when Amorolfine is combined with Azelnidipine.
Amphotericin B	The risk or severity of adverse effects can be increased when Amphotericin B is combined with Azelnidipine.

Metoprolol

Catecholamine Depleting Drugs

Catecholamine depleting drugs (e.g., reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with Metoprolol plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension

CYP2D6 Inhibitors

Drugs that are strong inhibitors of CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone were shown to double metoprolol concentrations. While there is no information about moderate or weak inhibitors, these too are likely to increase metoprolol concentration. Increases in plasma concentration decrease the cardio selectivity of metoprolol. Monitor patients closely when the combination cannot be avoided.

Digitalis, Clonidine, and Calcium Channel Blockers

Digitalis glycosides, clonidine, diltiazem, and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta-blockers can increase the risk of bradycardia. If clonidine and a beta-blocker, such as metoprolol are co-administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.

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

Azelnidipine

This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is diagnosed during administration, this drug should be discontinued immediately. (Foetal or neonatal death, oligohydramnios, foetal or neonatal hypotension, renal failure, hyperkalaemia, skull hypoplasia, and extremity contracture/malformation of brain, skull, or face/pulmonary dysplasia possibly caused by oligohydramnios, etc. have been reported in pregnant patients in their second or third trimester treated with ARBs including this drug or ACE inhibitors. An overseas retrospective epidemiological study suggested that the relative risk of foetal malformation during the first trimester was higher in the group of ACE inhibitor users than the group of antihypertensive drug nonusers).

There is no specific information available for use in special populations.

Metoprolol

Pregnancy

Risk Summary

Untreated hypertension and heart failure during pregnancy can lead to adverse outcomes for the mother and the fetus (see Clinical Considerations). Available data from published observational studies have not demonstrated a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with metoprolol use during pregnancy. However, there are inconsistent reports of intrauterine growth restriction, preterm birth, and perinatal mortality with maternal use of beta-blockers, including metoprolol, during pregnancy (see Data). In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, approximately 24 times the daily dose of 200 mg in a 60-kg patient on a mg/m2 basis. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical consideration Disease-associated maternal and/or embryo/fetal risk Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature

delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. There is a risk for preterm birth with pregnant women with chronic heart failure in 3rd trimester of pregnancy.

Fetal/Neonatal adverse reactions

Metoprolol crosses the placenta. Neonates born to mothers who are receiving metoprolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates and manage accordingly.

Human Data

Data from published observational studies did not demonstrate an association of major congenital malformations and use of metoprolol in pregnancy. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth, and perinatal mortality with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitively establish or exclude any drug-associated risk during pregnancy.

Animal Data

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, i.e., 24 times, on a mg/m2 basis, the daily dose of 200 mg in a 60-kg patient. No fetal abnormalities were observed when pregnant rats received metoprolol orally up to a dose of 200 mg/kg/day, i.e., 10 times, the daily dose of 200 mg in a 60-kg patient.

Lactation

Risk Summary

Untreated hypertension and heart failure during pregnancy can lead to adverse outcomes for the mother and the fetus (see Clinical Considerations). Available data from published observational studies have not demonstrated a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with metoprolol use during pregnancy. However, there are inconsistent reports of intrauterine growth restriction, preterm birth, and perinatal mortality with maternal use of beta-blockers, including metoprolol, during pregnancy (see Data). In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, approximately 24 times the daily dose of 200 mg in a 60-kg patient on a mg/m2 basis. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical consideration Disease-associated maternal and/or embryo/fetal risk Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and

managed accordingly. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. There is a risk for preterm birth with pregnant women with chronic heart failure in 3rd trimester of pregnancy.

Fetal/Neonatal adverse reactions

Metoprolol crosses the placenta. Neonates born to mothers, who are receiving metoprolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates and manage accordingly.

Human Data

Data from published observational studies did not demonstrate an association of major congenital malformations and use of metoprolol in pregnancy. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth, and perinatal mortality with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitively establish or exclude any drug-associated risk during pregnancy.

Animal Data

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, i.e., 24 times, on a mg/m2 basis, the daily dose of 200 mg in a 60-kg patient. No fetal abnormalities were observed when pregnant rats received metoprolol orally up to a dose of 200 mg/kg/day, i.e., 10 times, the daily dose of 200 mg in a 60-kg patient.

Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of Metoprolol (0.2, 1or 2 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary endpoint (dose response for reduction in SBP). Some pre-specified secondary endpoints demonstrated effectiveness including:

• Dose-response for reduction in DBP,

• 1 mg/kg vs. placebo for change in SBP, and

• 2 mg/kg vs. placebo for change in SBP and DBP.

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals No clinically relevant differences in the adverse event profile were observed for pediatric patients aged 6 to 16 years as compared with adult patients. Safety and effectiveness of Metoprolol have not been established in patients < 6 years of age.

Geriatric Use

Clinical studies of Metoprolol in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

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 such as Telmisartan.

Since the antihypertensive activity of Azelnidipine may in-duce dizziness, etc., patients should be cautioned to pay much attention in engaging in potentially hazardous activities such as working at a height and driving a car.

4.8. Undesirable effects

Azelnidipine

The most commonly reported includes rash and itch.

The symptoms described below are rarely seen as initial symptoms of the adverse reactions indicated in brackets. If any of these symptoms occur, stop taking this medicine and see your doctor immediately.

• General malaise, loss of appetite, yellowness of skin and white of eye [hepatic dysfunction, jaundice]

• Dizziness, light-headedness [atrioventricular block, sinus arrest, bradycardia] The above symptoms do not describe all the adverse reactions to this medicine.

Hepatic function disorder, jaundice: Hepatic function disorder with elevations of AST (GOT), ALT (GPT), γ-GTP, and jaundice may occur. Patients should be closely monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Metoprolol

The following adverse reactions are described elsewhere in labeling:

• Worsening angina or myocardial infarction

• Worsening heart failure

• Worsening AV block

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Hypertension and Angina: Most adverse reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia, and rash. Heart Failure: In the MERIT-HF study comparing Metoprolol in daily doses up to 200 mg (mean dose 159 mg once daily; n=1990) to placebo (n=2001), 10.3% of Metoprolol patients discontinued for adverse reactions vs. 12.2% of placebo patients. The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of ≥ 1% in the Metoprolol group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Reactions Occurring in the MERIT-HF Study at an Incidence ≥1% in the Metoprolol Group and Greater Than Placebo by More Than 0.5%.

	Metoprolol n=1990 % of patients	**Placebo n=2001 % of patients**
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4

Post-operative Adverse Events:

In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta–blocker therapy, Metoprolol 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day. Metoprolol use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1.0% vs. 0.5%; HR 2.17; 95% CI 1.26, 3.74) and death (3.1% vs. 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo.

Reporting of adverse reactions

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: https://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.

4.9. Overdose

Azelnidipine

Azelnidipine overdose may cause hypotension.

The hypotensive effect was preceded by an increase in plasma drug concentration and it persisted even after plasma drug concentration declined to very low levels. In the isolated arteries, the calcium blocking action developed gradually after treatment with azelnidipine and survived for a long period of time after the drug was removed from the bathing solution. These data suggest that the high affinity to vascular tissue contributes to the long-lasting hypotensive effects of this agent. The results from clinical studies in hypertensive patients indicated that once daily administration of azelnidipine achieved stable, 24-h control of blood pressure with no change or a slight decrease in heart rate. Clinical studies also showed a low incidence of adverse events such as headache, facial flush, dizziness, and palpitations. These characteristics make azelnidipine a new generation calcium antagonist that can be used for the treatment of hypertension.

Metoprolol

Signs and Symptoms - Overdosage of Metoprolol may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting. Treatment – Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures: Hemodialysis is unlikely to make a useful contribution to metoprolol elimination. Bradycardia: Evaluate the need for atropine, adrenergic-stimulating drugs, or pacemaker to treat bradycardia and conduction disorders. Hypotension: Treat

underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine. Heart failure and shock: May be treated when appropriate with suitable volume expansion, injection of glucagon (if necessary, followed by an intravenous infusion of glucagon), intravenous administration of adrenergic drugs such as dobutamine, with α1 receptor agonistic drugs added in presence of vasodilation. Bronchospasm: Can usually be reversed by bronchodilators.

5. Pharmacological properties

5.1. Mechanism of Action

Azelnidipine

Azelnidipine 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 Ca^{2+} influx through the voltage-dependent channels of smooth muscles in vascular walls).

Metoprolol

Metoprolol is a beta1-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

5.2. Pharmacodynamic properties

Azelnidipine

Pharmacotherapeutic group: Calcium channel blockers – Dihydropyridine derivatives. Azelnidipine is a third generation; long-acting dihydropyridine (DHP) based calcium channel blocker (CCB). It 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.

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.

Metoprolol

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by

- Reduction in heart rate and cardiac output at rest and upon exercise,
- reduction of systolic blood pressure upon exercise,
- Inhibition of isoproterenol-induced tachycardia, and
- Reduction of reflex orthostatic tachycardia. The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Beta1-blocking effects in the range of 30-80% of the maximal effect (approximately 8 to

23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30 to 540 nmol/L. The relative beta1-selectivity of metoprolol diminishes and blockade of beta2-adrenoceptors increases at plasma concentration above 300 nmol/L.

5.3 Pharmacokinetic properties

Azelnidipine

Oral ingestion of azelnidipine demonstrates rapid and dose-dependent absorption. After multiple-dose of Azelnidipine 8 mg/day for 7 days, Cmax 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. In a Chinese study examining the pharmacokinetics of the drug, the volume of distribution was found to be 1749 +/- 964. Azelnidipine is widely bound to human plasma proteins (90%–91%). 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.

In one study, following a single 4mg oral dose of 14C-labeled azelnidipine in humans, about 26% of the drug was thought to be excreted in the urine and 63% in the feces during the 1-week period post administration.

Half-life of azelnidipine: 16 –28 hours.

Metoprolol

Absorption

The peak plasma levels following once-daily administration of Metoprolol average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Metoprolol, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Metoprolol administration. The peak plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Distribution

Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

Metabolism

Metoprolol is a racemic mixture of R- and S- enantiomers and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.

Elimination

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged

in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Azelnidipine

No information available.

Metoprolol

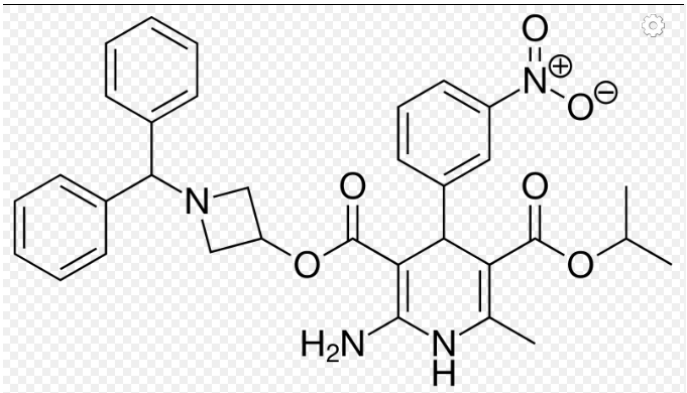
Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m2 basis, the daily dose of 200 mg in a 60-kg patient.

7. Description

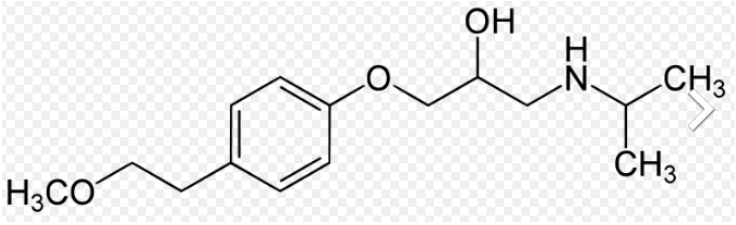
<u>Azelnidipine:</u>

Azelnidipine is 3-1-Benzhydryl-3-azetidinyl 5-isopropyl 2-amino-6-methyl-4-(m-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. The Empirical formula is $C_{33}H_{34}N_4O_6$ and its molecular weight is 582.64 g/mol. The structural formula is:



Metoprolol:

Metoprolol (RS)-1-[4-(2-Methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol. The Empirical formula $C_{15}H_{25}NO_3$ and its molecular weight is 267.364 g/mol. The structural formula is:



8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

UNIAZ BETA is available in pack of 10 Tablet.

8.4. Storage and handing instructions

Store in a dry and dark place not exceeding 30°C.

Keep the medicine out of reach of children

Tablet should be swallowed whole & not to be chewed or crushed.

9. Patient Counselling Information

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

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd.

19, 20 & 21, Sector-6A,

I.I.E., SIDCUL, Ranipur,

Haridwar-249 403, Uttarakhand.

11. Details of permission or licence number with date

Mfg. Licence. No.: 10/UA/2004 Issued on: 19.01.2024

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ UNIAZ BETA 8 mg +25 mg & 8 mg+50 mg, 16 mg +25 mg & 16 mg+50 mg/MAY-2024/01/PI