PRESCRIBING INFORMATION

For the use of a registered medical practitioner or a hospital or a laboratory only

Azilsartan Medoxomil and Cilnidipine Tablets

MYOTAN® CN 40/10

COMPOSITION

Each film coated tablet contains:

Azilsartan Kamedoxomil
Equivalent to Azilsaratan Medoxomil……40 mg
Cilnidipine IP…….10 mg
Excipients…….q.s.
Colours: Tartrazine Lake and Titanium Dioxide IP

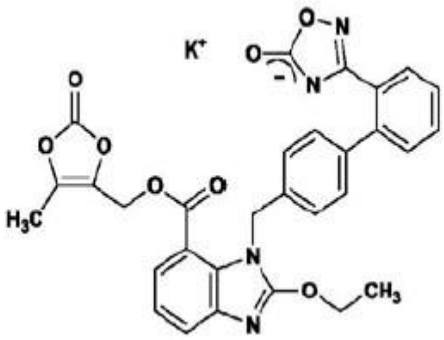
DESCRIPTION

Azilsartan medoxomil, a prodrug, is hydrolyzed to Azilsartan in the gastrointestinal tract during absorption. Azilsartan is a selective AT1 subtype angiotensin II receptor antagonist. Cilnidipine is a calcium channel blocker. It is a calcium antagonist accompanied with L-type and N-type calcium channel blocking functions.

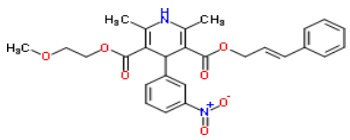
The potassium salt of azilsartan medoxomil, Azilsartan kamedoxomil, is chemically described as (5Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4yl]methyl}-1H-benzimidazole-7-carboxylate monopotassium salt. Its empirical formula is $C_{30}H_{23}KN_4O_8$.

Cilnidipine is chemically described as 3-O-(2-methoxyethyl) 5-O-[(E)-3-phenylprop-2-enyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate Its empirical formula is $C_{27}H_{28}N_2O_7$

The structural formula for azilsartan medoxomil is:



The Structural formula for Cilnidipine is:



INDICATIONS

It is indicated for the treatment of hypertension, to lower blood pressure.

DOSAGE AND ADMINISTRATION

- Starting dose is 40/5 mg once daily
- The recommended adult oral dosage of Cilnidipine is 5-10 mg once daily.
- Dose may be increased to 40/10 mg after 2 to 4 weeks as needed to achieve blood pressure goals
- Maximal dose is 40/10 mg
- May be administered with other antihypertensive agents

USE IN SPECIAL POPULATION

Pregnancy

Use of drugs that affect the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue this drug as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the rennin angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue this formulation, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Edarbyclor for hypotension, oliguria, and hyperkalemia.

Nursing Mothers:

*Azilsartan:*It is not known if azilsartan is excreted in human milk, but azilsartan is excreted at low concentrations in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Cilnidipine : No information is available regarding the use in pregnancy and lactation. Physician's advice should be followed.

Pediatric Use

Safety and effectiveness of drug in pediatric patients under 18 years of age has not been established. If oliguria or hypotension occurs, support blood pressure and renal function. Exchange transfusions or dialysis may be required.

Geriatric Use

No dose adjustment with Azilsartan is necessary in elderly patients. Of the total patients in clinical studies with Azilsartan, 26% were elderly (65 years of age and older); 5% were 75 years of age and older. Abnormally high serum creatinine values were more likely to be reported for patients age 75 or older. No other differences in safety or effectiveness were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Dose adjustment is not required in patients with mild-to-severe renal impairment or end-stage renal disease. Patients with moderate to severe renal impairment are more likely to report abnormally high serum creatinine values.

CONTRA-INDICATION

Azilsartan: Do not coadminister aliskiren-containing products with Azilsartan in patients with diabetes

Cilnidipine: Cilnidipine is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to Cilnidipine or any other component of this product.

WARNINGS AND PRECAUTIONS

Azilsartan

Fetal Toxicity

Azilsartan medoxomil: Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Azilsartan as soon as possible.

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Azilsartan. Correct volume or salt depletion prior to administration of Azilsartan, or start treatment at 40 mg. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of

normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with Azilsartan. In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. There has been no long-term use of azilsartan in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Cilnidipine:

Cilnidipine is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to Cilnidipine or any other component of this product.

DRUG INTERACTIONS

Azilsartan

No clinically significant drug interactions have been observed in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, and warfarin. Therefore, it may be used concomitantly with these medications.

Non-steroidal Anti-Inflammatory Agents, including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including azilsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving azilsartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including azilsartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on Edarbi and other agents that affect the RAS.

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor agonists. Monitor serum lithium levels during concomitant use.

Cilnidipine

Cilnidipine can interact with aldesleukin, quinidine, phenytoin, rifampicin, erythromycin, other anti-hypertensive drugs and anti-psychotic drugs.

UNDESIRABLE EFFECT

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.
Check with your doctor immediately if any of the following side effects occur:

- feeling like you might pass out
- urinating less than usual or not at all
- drowsiness, confusion, mood changes, increased thirst, loss of appetite
- swelling, weight gain, feeling short of breath; or
- electrolyte imbalance (dry mouth, extreme thirst, drowsiness, restless feeling, confusion, increased or decreased urination, constipation, muscle pain or weakness, fast heart rate, or seizure (convulsions)).

❖ Other common side effects may include

❖ mild skin rash
❖ diarrhea, nausea, upset stomach;
❖ cough
❖ mild dizziness; or
❖ Weakness, tired feeling.

OVERDOSAGE

Azilsartan Medoxomil: Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once daily doses up to 320 mg of Azilsartan medoxomil were administered for 7 days and were well tolerated. In the event of an overdose, supportive therapy should be instituted as dictated by the patient's clinical status. Azilsartan is not dialyzable.
Cilnidipine: No clinical data is available.

CLINICAL PHARMACOLOGY

Mechanism of Action

Azilsartan target two separate mechanisms involved in blood pressure regulation. Azilsartan blocks the vasoconstriction and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells.
Cilnidipine is a novel dihydropyridine calcium antagonist and its calcium antagonistic activity is lasting longer than those of Nifedipine and Nicardipine. It inhibits cellular influx of calcium, thus causing vasodilatation. It has greater selectivity for vascular smooth muscle. It has little or no action at the SA or AV nodes and -ve inotropic activity is rarely seen at therapeutic doses.

Cilnidipine has been used for the treatment of hypertension and hypertensive associated vascular disorders. Cilnidipine has a very low solubility (BCS Class-II drug Low solubility high permeability) and compliance to the medication is always very poor.

PHARMACODYNAMICS

Azilsartan inhibits the pressor effects of an angiotensin II infusion in a dose-related manner. An azilsartan single dose equivalent to 32 mg azilsartan medoxomil inhibited the maximal pressor effect by approximately 90% at peak, and approximately 60% at 24 hours. Plasma angiotensin I and II concentrations and plasma renin activity increased while plasma aldosterone concentrations decreased after single and repeated administration of Azilsartan to healthy subjects; no clinically significant effects on serum potassium or sodium were observed.
Effect on Cardiac Repolarization: A thorough QT/QTc study was conducted to assess the potential of azilsartan to prolong the QT/QTc interval in healthy subjects. There was no evidence of QT/QTc prolongation at a dose of 320 mg of Azilsartan.

Cilnidipine :
A pharmacodynamic assessment study showed, all treatment groups, both SBP and DBP were decreased after a single administration of cilnidipine or valsartan alone and in combination. The greatest decreases in both SBP and DBP were seen at approximately 6 hours after study drug administration, when coadministered cilnidipine and valsartan resulted in a 2.9-fold significantly larger decrease in SBP (14.7 vs. 5.0 mmHg for SBP) and a 2.1-fold significantly larger decrease in DBP than did cilnidipine alone (16.3 vs. 7.9 mmHg for DBP)

PHARMACOKINETICS

Azilsartan medoxomil

Absorption:
Azilsartan medoxomil is rapidly hydrolyzed to azilsartan, the active metabolite, in the gastrointestinal tract during absorption. Azilsartan medoxomil is not detected in plasma after oral administration. Dose proportionality in exposure was established for azilsartan in the azilsartan medoxomil dose range of 20 mg to 320 mg after single or multiple dosing. The estimated absolute bioavailability of azilsartan following administration of azilsartan medoxomil is approximately 60%. After oral administration of azilsartan medoxomil, peak plasma concentrations (Cmax) of azilsartan are reached within 1.5 to 3 hours. Food does not affect the bioavailability of azilsartan.

Distribution

Azilsartan medoxomil: The volume of distribution of azilsartan is approximately 16L. Azilsartan is highly bound to human plasma proteins (>99%), mainly serum albumin. Protein binding is constant at azilsartan plasma concentrations well above the range achieved with recommended doses. In rats, minimal azilsartan-associated radioactivity crossed the blood-brain barrier. Azilsartan passed across the placental barrier in pregnant rats and was distributed to the fetus.

Metabolism and Elimination

Azilsartan medoxomil: Azilsartan is metabolized to two primary metabolites. The major metabolite in plasma is formed by O-dealkylation, referred to as metabolite M-II, and the minor metabolite is formed by decarboxylation, referred to as metabolite M-I. Systemic exposures to the major and minor metabolites in humans were approximately 50% and less than 1% of azilsartan, respectively. M-I and MII do not contribute to the pharmacologic activity of azilsartan medoxomil. The major enzyme responsible for azilsartan metabolism is CYP2C9. Following an oral dose of 14C-labeled azilsartan medoxomil, approximately 55% of radioactivity was recovered in feces and approximately 42% in urine, with 15% of the dose excreted in urine as azilsartan. The elimination half-life of azilsartan is approximately 11 hours and renal clearance is approximately 2.3 ml/min. Steady-state levels of azilsartan are achieved within 5 days and no accumulation in plasma occurs with repeated once-daily dosing.

Cilnidipine:

A PK analysis study with 51 subjects was planned. The mean plasma concentration–time profiles of cilnidipine after a single oral administration at 10 mg did not significantly differ when it was administered alone and when it was co-administered with valsartan 160 mg. For example, the total exposure to cilnidipine was comparable, i.e., the GMR (90% confidence interval [CI]) of Cmax and AUC for cilnidipine with and without valsartan was 0.91 (0.83–1.00) and 1.04 (0.98–1.10), respectively, although cilnidipine was absorbed slightly slower when it was coadministered with valsartan than when it was administered alone (median tmax: 2.0 vs. 2.5 hours for cilnidipine alone and in combination, respectively

INCOMPATIBILITIES

Not applicable (As already discussed in drug interactions)

PACKAGING INFORMATION

Alu-Alu of blister packing

STORAGE AND HANDLING INSTRUCTIONS:

Store below 30°C, protected from light & moisture.

MANUFATURED IN INDIA BY:

SYNOKEM PHARMACEUTICALS LTD.
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