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

ZILSAR CH 40/12.5

1. Generic Name

Azilsartan Medoxomil & Chlorthalidone Tablets

2. Qualitative And Quantitative Composition

Each film coated tablet contains:

Azilsartan Kamedoxomil equivalent to Azilsartan Medoxomil……40mg

Chlorthalidone I.P. ……12.5mg

Excipients……...q.s.

Colours: Ferric Oxide USP-NF Yellow & Titanium Dioxide I.P.

The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Hydroxide, and Fumaric acid, Hydroxy Propyl Cellulose, Ferric Oxide Yellow, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 8000, Talc and Titanium Dioxide.

3. Dosage form and strength

Dosage Form: Coated Tablets

Strength: Azilsartan Medoxomil…….40mg, Chlorthalidone……..12.5mg

4. Clinical Particulars

4.1 Therapeutic Indication

For the treatment of mild to moderate hypertension in adults.

4.2 Posology and Method of Administration

Dosing Information

The recommended starting dose of Zilsar CH is 40/12.5 mg taken orally once daily. Most of the antihypertensive effect is apparent within 1 to 2 weeks.

Zilsar CH may be used to provide additional blood pressure lowering for patients not adequately controlled on ARB or diuretic monotherapy treatment. Patients not controlled with azilsartan medoxomil 80 mg may have an additional systolic / diastolic clinic blood pressure reduction of 13/6 mm Hg when switched to Zilsar CH 40/12.5 mg. Patients not controlled with chlorthalidone 25 mg may have an additional clinic blood pressure reduction of 10/7 mm Hg when switched to Zilsar CH 40/12.5 mg.

Zilsar CH may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure goals.

Patients titrated to the individual components (azilsartan medoxomil and chlorthalidone) may instead receive the corresponding dose of Zilsar CH.

Zilsar CH may be taken with or without food.

Zilsar CH may be administered with other antihypertensive agents as needed.

Prior to Dosing

Correct any volume depletion prior to administration of Zilsar CH, particularly in patients with impaired renal function or those treated with high doses of diuretics.

Patients who experience dose-limiting adverse reactions on chlorthalidone may be switched to Zilsar CH, initially with a lower dose of chlorthalidone

Handling Instructions

As Zilsar CH is moisture sensitive, dispense and store Zilsar CH in its original container to protect Zilsar CH from light and moisture.

4.3 Contraindications

Zilsar CH is contraindicated in patients with anuria

4.4 Special Warnings and Precautions for Use

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue Zilsar CH as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

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 Zilsar CH as soon as possible.

Chlorthalidone

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia**.**

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Zilsar CH. Such patients are probably not good candidates to start therapy with more than one drug; therefore, correct volume prior to administration of Zilsar CH. 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

Monitor for worsening renal function in patients with renal impairment. Consider withholding or discontinuing Zilsar CH if progressive renal impairment becomes evident.

Azilsartan medoxomil

As a consequence of inhibiting the renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with Zilsar CH. 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. Similar results may be anticipated in patients treated with Zilsar CH. 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 medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results are expected.

Chlorthalidone

In patients with renal disease, chlorthalidone may precipitate azotemia. If progressive renal impairment becomes evident, as indicated by increased blood urea nitrogen, consider withholding or discontinuing diuretic therapy.

4.5 Drugs Interactions

Zilsar CH

The pharmacokinetics of azilsartan medoxomil and chlorthalidone are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with other drugs and Zilsar CH, although studies have been conducted with azilsartan medoxomil and chlorthalidone.

Azilsartan medoxomil

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, azilsartan medoxomil 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, co-administration 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 Zilsar CH and NSAID therapy.

The antihypertensive effect of Zilsar CH may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Chlorthalidone

Lithium renal clearance is reduced by diuretics, such as chlorthalidone, increasing the risk of lithium toxicity. Consider monitoring lithium levels when using Zilsar CH.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Pregnancy

Pregnancy Category D

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 Zilsar CH as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most reported 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 renin 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 Zilsar CH, 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 Zilsar CH for hypotension, oliguria, and hyperkalemia.

Nursing Mothers

It is not known if azilsartan is excreted in human milk, but azilsartan is excreted at low concentrations in the milk of lactating rats and thiazide-like diuretics like chlorthalidone are excreted in human milk. 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.

Pediatric Use

Safety and effectiveness of Zilsar CH in pediatric patients under 18 years of age have not been established.

Neonates with a history of *in utero* exposure to Zilsar CH: If oliguria or hypotension occurs, support blood pressure and renal function. Exchange transfusions or dialysis may be required.

Geriatric Use

No dose adjustment with Zilsar CH is necessary in elderly patients of the total patients in reported clinical studies with Zilsar CH, 24% were elderly (65 years of age or older); 5.7% were 75 years and older. No overall 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

Safety and effectiveness of Zilsar CH in narrated study in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been established. No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) or moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment.
Chlorthalidone may precipitate azotemia.

Hepatic Impairment
Azilsartan medoxomil
No dose adjustment is necessary for subjects with mild or moderate hepatic impairment. Azilsartan medoxomil has not been studied in patients with severe hepatic impairment
Chlorthalidone
Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

4.7 Effects on Ability to Drive and Use Machines

Not stated

4.8 Undesirable Effects

The following potential adverse reactions with Zilsar CH, azilsartan medoxomil, or chlorthalidone and similar agents are included in more detail in the Warnings and Precautions section of the label:

- Fetal toxicity
- Hypotension in Volume- or Salt-Depleted Patients
- Impaired Renal Function
- Hypokalaemia
- Hyperuricemia

Clinical Trials Experience
In the reported data 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.
Azilsartan medoxomil plus chlorthalidone has been evaluated for safety in more than 3900 patients with hypertension; more than 700 patients were treated for at least 6 months and more than 280 for at least 1 year. Adverse reactions have generally been mild and transient in nature.
Common adverse reactions that occurred in the 8-week factorial design trial in at least 2% of Zilsar CH -treated patients and greater than azilsartan medoxomil or chlorthalidone are presented in Table 1.

Table 1. Adverse Reactions Occurring at an Incidence of ≥2% of azilsartan medoxomil plus chlorthalidone -treated Patients and > Azilsartan medoxomil or Chlorthalidone.

Preferred Term	Azilsartan medoxomil 20, 40, 80 mg (N=470)	Chlorthalidone 12.5, 25 mg (N=316)	Zilsar CH 40 / 12.5, 40 / 25 mg (N=302)
Dizziness	1.7%	1.9%	8.9%
Fatigue	0.6%	1.3%	2.0%

Study discontinuation because of adverse reactions occurred in 8.3% of patients treated with the recommended doses of azilsartan medoxomil plus chlorthalidone compared with 3.2% of patients treated with azilsartan medoxomil and 3.2% of patients treated with chlorthalidone. The most common reasons for discontinuation of therapy with azilsartan medoxomil plus chlorthalidone were serum creatinine increased (3.6%) and dizziness (2.3%).

The adverse reaction profile obtained from 52 weeks of open-label combination therapy with azilsartan medoxomil plus chlorthalidone was similar to that observed during the double-blind, active controlled trials.

In 3 double-blind, active controlled, titration studies, in which azilsartan medoxomil plus chlorthalidone was titrated to higher doses in a step-wise manner, adverse reactions and discontinuations for adverse events were less frequent than in the fixed-dose factorial trial.

Azilsartan medoxomil

A total of 4814 patients were evaluated for safety when treated with azilsartan medoxomil at doses of 20, 40 or 80 mg in clinical trials. This includes 1704 patients treated for at least 6 months, of these, 588 were treated for at least 1 year. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race.

Adverse reactions with a plausible relationship to treatment that have been reported with an incidence of ≥0.3% and greater than placebo in more than 3300 patients treated with azilsartan medoxomil in controlled trials are listed below:

Gastrointestinal Disorders: diarrhea, nausea General Disorders and Administration Site Conditions: asthenia, fatigue

Musculoskeletal and Connective Tissue Disorders: muscle spasm Nervous System Disorders: dizziness, dizziness postural Respiratory, Thoracic and Mediastinal Disorders: cough

Chlorthalidone

The following adverse reactions have been observed in clinical trials of chlorthalidone: rash, headache, dizziness, GI upset, and elevations of uric acid and cholesterol.

Clinical Laboratory Findings with Zilsar CH

In the factorial design trial, clinically relevant changes in standard laboratory parameters were uncommon with administration of the recommended doses of azilsartan medoxomil plus chlorthalidone.

Renal parameters:
Increased blood creatinine is a known pharmacologic effect of renin-angiotensin aldosterone system (RAAS) blockers, such as ARBs and ACE inhibitors, and is related to the magnitude of blood pressure reduction. The incidence of consecutive increases of creatinine ≥50% from baseline and >ULN was 2.0% in patients treated with the recommended doses of azilsartan medoxomil plus chlorthalidone compared with 0.4% and 0.3% with azilsartan medoxomil and chlorthalidone, respectively. Elevations of creatinine were typically transient, or non-progressive and reversible, and associated with large blood pressure reductions.
Mean increases in blood urea nitrogen (BUN) were observed with azilsartan medoxomil plus chlorthalidone (5.3 mg/dL) compared with azilsartan medoxomil (1.5 mg/dL) and with chlorthalidone (2.5 mg/dL).

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

Limited data are available related to overdosage in humans.
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.

Chlorthalidone
Symptoms of acute overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

The active ingredients of Zilsar CH 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. Chlorthalidone produces diuresis with increased excretion of sodium and chloride at the cortical diluting segment of the ascending limb of Henle's loop of the nephron.

Azilsartan medoxomil
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzymes (ACE, kinase II). Angiotensin II is the principle pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Azilsartan 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. Its action is, therefore, independent of the pathway for angiotensin II synthesis.
An AT2 receptor is also found in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Azilsartan has more than a 10,000-fold greater affinity for the AT1 receptor than for the AT2 receptor.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction catalysed by ACE. Because azilsartan does not inhibit ACE (kinase II), it should not affect bradykinin levels. Whether this difference has clinical relevance is not yet known. Azilsartan does not bind to or block other receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of azilsartan on blood pressure.

Chlorthalidone
Chlorthalidone produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect.

5.2 Pharmacodynamics Properties

Zilsar CH tablets have been shown to be effective in lowering blood pressure. Both azilsartan medoxomil and chlorthalidone lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

Azilsartan medoxomil
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 medoxomil to healthy subjects; no clinically significant effects on serum potassium or sodium were observed.

Chlorthalidone
The diuretic effect of chlorthalidone occurs in approximately 2.6 hours and continues for up to 72 hours.

5.3 Pharmacokinetic Properties

Following oral administration of azilsartan medoxomil plus chlorthalidone, peak plasma concentrations of azilsartan and chlorthalidone are reached at 3 and 1 hours, respectively.

The rate (Cmax and Tmax) and extent (AUC) of absorption of azilsartan are similar when it is administered alone or with chlorthalidone. The extent (AUC) of absorption of chlorthalidone is similar when it is administered alone or with azilsartan medoxomil; however, the Cmax of chlorthalidone from Zilsar CH was 47% higher. The elimination half-lives of azilsartan and chlorthalidone are approximately 12 hours and 45 hours, respectively.
There is no clinically significant effect of food on the bioavailability of azilsartan medoxomil plus chlorthalidone.

Azilsartan medoxomil
Absorption
Azilsartan medoxomil is rapidly hydrolysed 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
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. Chlorthalidone: In whole blood, chlorthalidone is predominantly bound to erythrocyte carbonic anhydrase. In the plasma, approximately 75% of chlorthalidone is bound to plasma proteins, 58% of the drug being bound to albumin.
Metabolism and Elimination
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.

Chlorthalidone
The major portion of the drug is excreted unchanged by the kidneys. Nonrenal routes of elimination have yet to be clarified. Data are not available regarding percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood-brain barrier.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of azilsartan medoxomil and chlorthalidone. However, these studies have been conducted for azilsartan medoxomil alone.

Azilsartan medoxomil

Carcinogenesis:

Azilsartan medoxomil was not carcinogenic when assessed in 26-week transgenic (Tg.rasH2) mouse and 2-year rat studies. The highest doses tested (450 mg azilsartan medoxomil/kg/day in the mouse and 600 mg azilsartan medoxomil/kg/day in the rat) produced exposures to azilsartan that are 12 (mice) and 27 (rats) times the average exposure to azilsartan in humans given the maximum recommended human dose (MRHD, 80 mg azilsartan medoxomil/day). M-II was not carcinogenic when assessed in 26-week Tg.rasH2 mouse and 2-year rat studies. The highest doses tested (approximately 8000 mg M-II/kg/day (males) and 11,000 mg M-II/kg/day (females) in the mouse and 1000 mg M-II/kg/day (males) and up to 3000 mg M-II/kg/day (females) in the rat) produced exposures that are, on average, about 30 (mice) and 7 (rats) times the average exposure to M-II in humans at the MRHD.

Mutagenesis:

Azilsartan medoxomil, azilsartan, and M-II were positive for structural aberrations in the Chinese Hamster Lung Cytogenic Assay. In this assay, structural chromosomal aberrations were observed with the prodrug, azilsartan medoxomil, without metabolic activation. The active moiety, azilsartan, was also positive in this assay both with and without metabolic activation. The major human metabolite, M-II was also positive in this assay during a 24-hr assay without metabolic activation. Azilsartan medoxomil, azilsartan, and M-II were devoid of genotoxic potential in the Ames reverse mutation assay with Salmonella typhimurium and Escherichia coli, the in vitro Chinese Hamster Ovary Cell forward mutation assay, the in vitro mouse lymphoma (tk) gene mutation test, the ex vivo unscheduled DNA synthesis test, and the in vivo mouse and/or rat bone marrow micronucleus assay.

Impairment of Fertility:

There was no effect of azilsartan medoxomil on the fertility of male or female rats at oral doses of up to 1000 mg azilsartan medoxomil/kg/day [6000 mg/m2 (approximately 122 times the MRHD of 80 mg azilsartan medoxomil/60 kg on a mg/m2 basis)]. Fertility of rats also was unaffected at doses of up to 3000 mg M-II/kg/day.

Animal Toxicology and/or Pharmacology

The safety profiles of azilsartan medoxomil and chlorthalidone monotherapy have been individually established. To characterize the toxicological profile for azilsartan medoxomil plus chlorthalidone a 13-week repeat-dose toxicity study was conducted in rats. The results of this study indicated that the combined administration of azilsartan medoxomil, M-II, and chlorthalidone resulted in increased exposures to chlorthalidone. Pharmacologically-mediated toxicity, including suppression of body weight gain and decreased food consumption in male rats, and increases in blood urea nitrogen in both sexes, was enhanced by coadministration of azilsartan medoxomil, M-II, and

chlorthalidone. With the exception of these findings, there were no toxicologically synergistic effects in this study. In an embryo-fetal developmental study in rats, there was no teratogenicity or increase in fetal mortality in the litters of dams receiving azilsartan medoxomil, M-II and chlorthalidone concomitantly at maternally toxic doses.

Azilsartan medoxomil Reproductive Toxicology*:* In pre- and postnatal rat development reported studies, adverse effects on pup viability, delayed incisor eruption and dilatation of the renal pelvis along with hydronephrosis were seen when azilsartan medoxomil was administered to pregnant and nursing rats at 1.2 times the MRHD on a mg/m^2 basis. Reproductive toxicity studies indicated that azilsartan medoxomil was not teratogenic when administered at oral doses up to 1000 mg azilsartan medoxomil/kg/day to pregnant rats (122 times the MRHD on a mg/m^2 basis) or up to 50 mg azilsartan medoxomil/kg/day to pregnant rabbits (12 times the MRHD on a mg/m^2 basis). M-II also was not teratogenic in rats or rabbits at doses up to 3000 mg MII/kg/day. Azilsartan crossed the placenta and was found in the fetuses of pregnant rats and was excreted into the milk of lactating rats.

Chlorthalidone

Reproductive toxicology: Reproduction studies have been performed in the rat and the rabbit at doses up to 420 times the human dose and have revealed no evidence of harm to the fetus. Thiazides cross the placental barrier and appear in cord blood.

Pharmacology:

Biochemical studies in animals have suggested reasons for the prolonged effect of chlorthalidone. Absorption from the gastrointestinal tract is slow because of its low solubility. After passage to the liver, some of the drug enters the general circulation, while some is excreted in the bile, to be reabsorbed later. In the general circulation, it is distributed widely to the tissue, but is taken up in highest concentrations by the kidneys, where amounts have been found 72 hours after ingestion, long after it has disappeared from other tissues. The drug is excreted unchanged in the urine.

CLINICAL STUDIES

The antihypertensive effects of azilsartan medoxomil plus chlorthalidone have been demonstrated in a total of 5 randomized controlled reported studies, which included 4 double-blind, active-controlled studies and 1 open-label, long-term active-controlled study. The reported studies ranged from 8 weeks to 12 months in duration, at doses ranging from 20/12.5 mg to 80/25 mg once daily. A total of 5310 patients (3082 given azilsartan medoxomil plus chlorthalidone and 2228 given active comparator) with moderate or severe hypertension were studied. Overall, randomized patients had a mean age of 57 years, and included 52% males, 72% whites, 21% blacks, 15% with diabetes, 70% with mild or moderate renal impairment, and a mean BMI of 31.6 kg/m^2.An 8-week, multicentre, randomized, double-blind, active-controlled, parallel group factorial trial in patients with moderate to severe hypertension compared the effect on blood pressure of azilsartan medoxomil plus chlorthalidone with the respective monotherapies. The trial randomized 1714 patients with baseline systolic blood pressure between 160 and 190 mm Hg (mean 165 mm Hg) and a baseline diastolic blood pressure <119 mm Hg (mean 95 mm Hg) to one of the 11 active treatment arms.

The 6 treatment combinations of azilsartan medoxomil 20, 40, or 80 mg and chlorthalidone 12.5 or 25 mg resulted in statistically significant reduction in systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (ABPM) (Table 2) and clinic measurement (Table 3) at trough compared with the respective individual monotherapies. The clinic blood pressure reductions appear larger than those observed

with ABPM, because the former include a placebo effect, which was not directly measured. Most of the antihypertensive effect of azilsartan medoxomil plus chlorthalidone occurs within 1-2 weeks of dosing. The blood pressure lowering effect was maintained throughout the 24-hour period (Figure 1).

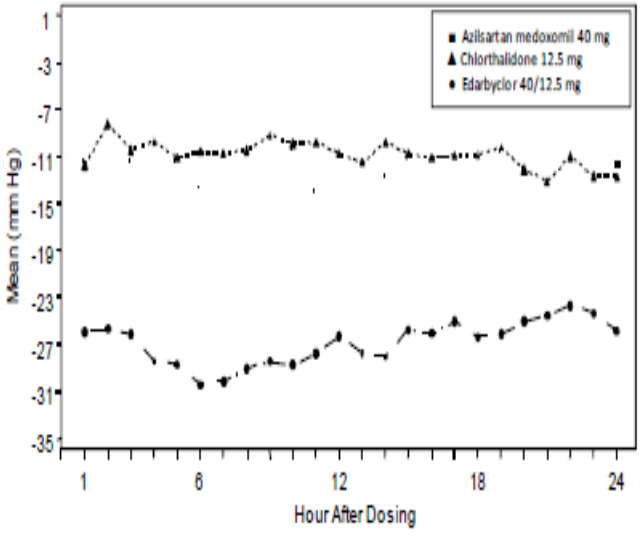
Table 2. Mean Change from Baseline in Systolic/Diastolic Blood Pressure (mm Hg) as Measured by ABPM at Trough (22-24 Hours Post-Dose) at Week 8: Combination Therapy vs Monotherapy

Chlorthalidone, mg	Azilsartan Medoxomil, mg			
	0	20	40	80
0	N/A	-12 / -8	-13 / -7	-15 / -9
12.5	-13 / -7	-23 / -13	-24 / -14	-26 / -17
25	-16 / -8	-26 / -15	-30 / -17	-28 / -16

Table 3. Mean Change from Baseline in Clinic Systolic/Diastolic Blood Pressure (mm Hg) at Week 8: Combination Therapy vs Monotherapy

Chlorthalidone, mg	Azilsartan Medoxomil, mg			
	0	20	40	80
0	N/A	-20 / -7	-23 / -9	-24 / -10
12.5	-21 / -7	-34 / -14	-37 / -16	-37 / -17
25	-27 / -9	-37 / -16	-40 / -17	-40 / -19

Figure 1. Mean Change from Baseline at Week 8 in Ambulatory Systolic Blood Pressure (mm Hg) by Treatment and Hour



Azilsartan medoxomil plus chlorthalidone was effective in reducing blood pressure regardless of age, gender, or race.

Azilsartan medoxomil plus chlorthalidone was effective in treating black patients (usually a low-renin population). In a 12-week, double-blind forced-titration trial, azilsartan medoxomil plus chlorthalidone 40/25 mg was statistically superior (P<0.001) to olmesartan medoxomil – hydrochlorothiazide (OLM/HCTZ) 40/25 mg in reducing systolic blood pressure in patients with moderate to severe hypertension.

Table 4 Similar results were observed in all subgroups, including age, gender, or race of patients.

	Zilsar CH 40/25 mg N=355	OLM/HCTZ 40/25 mg N=364
Clinic (Mean Baseline 165/96 mm Hg)	-43 / -19	-37 / -16
Trough by ABPM (22-24 hours) (Mean Baseline 153/92 mm Hg)	-33 / -20	-26 / -16

azilsartan medoxomil plus chlorthalidone lowered blood pressure more effectively than OLM/HCTZ at each hour of the 24-hour interposing period as measured by ABPM.

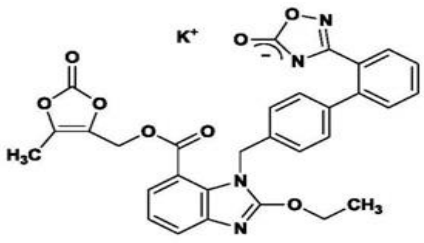
Cardiovascular Outcomes

There are no trials of azilsartan medoxomil plus chlorthalidone demonstrating reductions in cardiovascular risk in patients with hypertension; however, trials with chlorthalidone and at least one drug pharmacologically similar to azilsartan medoxomil have demonstrated such benefits.

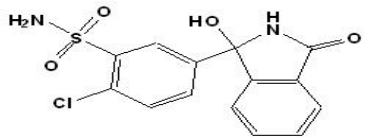
7. DESCRIPTION

Azilsartan Kamedoxomil

The potassium salt of azilsartan medoxomil, azilsartan kamedoxomil, is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate monopotassium salt. Its empirical formula is $C_{30}H_{23}KN_4O_8$ with a molecular weight of 606.62. The structural formula for azilsartan medoxomil is:



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



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

Azilsartan Medoxomil & Chlorthalidone Tablets are light yellow coloured, circular film coated tablets plain on both sides. The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Hydroxide, Fumaric acid, Hydroxy Propyl Cellulose, Ferric Oxide Yellow, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 8000, Talc and Titanium Dioxide.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Zilsar CH 40/12.5 is available in Blister pack of 10 tablets.

8.4 Storage and Handing Instructions

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

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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

1. What **Zilsar CH is** and what it is used for
2. What you need to know before you take **Zilsar CH**
3. How to take **Zilsar CH**
4. Possible side effects
5. How to store **Zilsar CH**
6. Contents of the pack and other information

9.1 What Zilsar CH is and what it is used for

Zilsar CH is a prescription medicine that contains azilsartan medoxomil, an angiotensin receptor blocker (ARB) and chlorthalidone, a water pill (diuretic).

Zilsar CH is used For the treatment of mild to moderate hypertension in adults.

It is not known if Zilsar CH is safe and effective in children under 18 years of age.

9.2 What you need to know before you take Zilsar CH

Do not take Zilsar CH if you:

• make less urine because of kidney problems

What should I tell my doctor before taking Zilsar CH?

Before you take Zilsar CH, tell your doctor if you:

- have been told that you have abnormal body salt (electrolytes) levels in your blood
- have liver or kidney problems
- have heart problems or stroke
- are vomiting or have diarrhea
- have gout
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed? It is not known if Zilsar CH passes into your breast milk. You and your doctor should decide if you will take Zilsar CH or breastfeed. You should not do both. Talk with your doctor about the best way to feed your baby if you take Zilsar CH.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- Other medicines used to treat your high blood pressure or heart problem
- water pills (diuretics)
- lithium carbonate (Lithobid), lithium citrate
- digoxin (Lanoxin)

Ask your doctor if you are not sure if you are taking a medicine listed above. Know the medicines you take. Keep a list of them and show it to your doctor or pharmacist when you get a new medicine.

9.3. How to take Zilsar CH

- Take Zilsar CH exactly as your doctor tells you to.
- Your doctor will tell you how much Zilsar CH to take and when to take it.
- Your doctor may prescribe other medicines for you to take along with Zilsar CH to treat your high blood pressure.
- Zilsar CH can be taken with or without food.
- If you miss a dose, take it later in the same day. Do not take more than 1 dose of Zilsar CH in a day.
- If you take too much Zilsar CH and have symptoms of low blood pressure (hypotension) and dizziness, call your doctor for advice. See "What are the possible side effects of Zilsar CH?"

9.4 Possible side effects

Like all medicines, Zilsar CH can cause side effects, although not everybody gets them

Zilsar CH may cause serious side effects, including:

- **Low blood pressure (hypotension) and dizziness** is most likely to happen if you also:

• take water pills (diuretics)

• are on a low-salt diet

- take other medicines that affect your blood pressure
- sweat a lot
- get sick with vomiting or diarrhea
- do not drink enough fluids

If you feel faint or dizzy, lie down and call your doctor right away. If you pass out (faint) have someone call your doctor or get medical help. Stop taking Zilsar CH.

Kidney problems. Kidney problems may become worse in people that already have kidney disease. Some people have changes in blood tests for kidney function and may need a lower dose of Zilsar CH or may need to stop treatment with Zilsar CH. During treatment with Zilsar CH , certain people who have severe heart failure, narrowing of the artery to the kidney, or who lose too much body fluid such as with nausea, vomiting, bleeding, or trauma, may develop sudden kidney failure and in rare instances, death.

Fluid and body salt (electrolyte) problems. Tell your doctor if you get any of the following symptoms:

- dry mouth
- confusion
- passing very little urine or thirst
- seizures passing large amounts of lack of energy (lethargic)
- muscle pain or cramps urine weakness
- restlessness
- fast or abnormal heartbeat drowsiness
- muscle tiredness (fatigue)
- nausea and vomiting
- constipation

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

9.5. How to store Zilsar CH

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

Keep all medicines out of reach of children.

9.6. Contents of the pack and other information

Active ingredients*:* azilsartan medoxomil and chlorthalidone

The excipients used are Mannitol, Microcrystalline Cellulose, Sodium Hydroxide, Fumaric acid, Hydroxy Propyl Cellulose, Ferric Oxide Yellow, Crospovidone, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 8000, Talc and Titanium Dioxide.

10. DETAILS OF MANUFACTURER

Manufactured by:
Hetero Labs Limited (Unit II)
Kalyanpur (Village), Chakkan Road, Baddi (Tehsil),

Solan (Distt.), Himachal Pradesh – 173205.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. MNB/09/780 issued on 09.07.2018.

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ Zilsar CH 40, 12.5mg/FEB-20/01/PI