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

ZILSAR

1. Generic name

Azilsartan Medoxomil Tablets

2. Qualitative and quantitative composition

ZILSAR 40

Each uncoated tablet contains

Azilsartan Kamedoxomil

Eq.to Azilsartan Medoxomil….40 mg

Excipients……..q.s.

ZILSAR 80

Each uncoated tablet contains:

Azilsartan Kamedoxomil

Eq.to Azilsartan Medoxomil…….80 mg

Excipients……..q.s.

3. Dosage form and strength

Dosage Form: Uncoated Tablet

Strength: 40mg & 80mg

4. Clinical particulars

4.1 Therapeutic Indications

Azilsartan is indicated for the treatment of hypertension in adult patient, either alone or in combination with other antihypertensive agents.

4.2 Posology and Method of Administration

As directed by the Cardiologist.

Posology

The recommended starting dose is 40 mg once daily. The dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose.

Near-maximal antihypertensive effect is evident at 2 weeks, with maximal effects attained by 4 weeks.

If blood pressure is not adequately controlled with Azilsartan Medoxomilalone, additional blood pressure reduction can be achieved when this treatment is coadministered with other antihypertensive medicinal products, including diuretics (such as chlortalidone and hydrochlorothiazide) and calcium channel blockers.

Special populations

Elderly (65 years and over)

No initial dose adjustment with Azilsartan Medoxomil is necessary in elderly patients, although consideration can be given to 20 mg as a starting dose in the very elderly (≥ 75 years), who may be at risk of hypotension.

Renal impairment

Caution should be exercised in hypertensive patients with severe renal impairment and end stage renal disease as there is no experience of use of Azilsartan Medoxomil in these patients. Hemodialysis does not remove azilsartan from the systemic circulation.

No dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment

Azilsartan Medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group.

As there is limited experience of use of Azilsartan Medoxomil in patients with mild to moderate hepatic impairment close monitoring is recommended and consideration should be given to 20 mg as a starting dose.

Intravascular volume depletion

For patients with possible depletion of intravascular volume or salt depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics), Azilsartan Medoxomil should be initiated under close medical supervision and consideration can be given to 20 mg as a starting dose.

Black population

No dose adjustment is required in the black population, although smaller reductions in blood pressure are observed compared with a non-black population. This generally has been true for other angiotensin II receptor (AT_1) antagonists and angiotensin-converting enzyme inhibitors. Consequently, uptitration of Azilsartan Medoxomil and concomitant therapy may be needed more frequently for blood pressure control in black patients.

Paediatric population

The safety and efficacy of Azilsartan Medoxomil in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Method of administration

Azilsartan Medoxomil is for oral use and may be taken with or without food.

4.3 Contraindications

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

- Second and third trimester of pregnancy.

- The concomitant use of Azilsartan Medoxomil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2).

4.4 Special Warnings and Precautions for Use

Activated renin-angiotensin-aldosterone system (RAAS)

In patients whose vascular tone and renal function depend predominantly on the activity of the RAAS (e.g. patients with congestive heart failure, severe renal impairment or renal artery stenosis), treatment with medicinal products that affect this system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, has been

associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with Azilsartan Medoxomil.

Caution should be exercised in hypertensive patients with severe renal impairment, congestive heart failure or renal artery stenosis, as there is no experience of use of Azilsartan Medoxomil in these patients.

Excessive blood pressure decreases in patients with ischaemic cardiomyopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Dual blockade of the RAAS

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Kidney transplantation

There is currently no experience on the use of Azilsartan Medoxomil in patients who have recently undergone kidney transplantation.

Hepatic impairment

Azilsartan Medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group.

Hypotension in volume- and /or salt-depleted patients

In patients with marked volume- and/or salt-depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Azilsartan Medoxomil. Hypovolemia should be corrected prior to administration of Azilsartan Medoxomil, or the treatment should start under close medical supervision, and consideration can be given to a starting dose of 20 mg.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the RAAS. Therefore, the use of Azilsartan Medoxomil is not recommended in these patients.

Hyperkalaemia

Based on experience with the use of other medicinal products that affect the RAAS, concomitant use of Azilsartan Medoxomil with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients. In the elderly, in patients with renal insufficiency, in diabetic patients and/or in patients with other co-morbidities, the risk of hyperkalaemia, which may be fatal, is increased. Monitoring of potassium should be undertaken as appropriate.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

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.

Lithium

As with other angiotensin II receptor antagonists the combination of lithium and Azilsartan Medoxomil is not recommended.

4.5 Drug-Interactions

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of lithium and angiotensin-converting enzyme inhibitors. A similar effect may occur with angiotensin II receptor antagonists. Due to the lack of experience with concomitant use of azilsartan medoxomil and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Caution required with concomitant use

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid > 3 g/day), and non-selective NSAIDs

When angiotensin II receptor antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II receptor antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, adequate hydration and monitoring of renal function at the beginning of the treatment are recommended.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of serum potassium should be undertaken as appropriate.

Additional information

Clinical trial data has shown that dual blockade of the 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.

No clinically significant interactions have been reported in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlortalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, and warfarin.

Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastrointestinal tract and/or during drug absorption. *In vitro* studies indicated that interactions based on esterase inhibition are unlikely.

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

Pregnancy

WARNING: FETAL TOXICITY

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

There are no data from the use of azilsartan medoxomil in pregnant women. Studies in animals have shown reproductive toxicity.

Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there are 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 therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia).

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

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

Breast-feeding

Because no information is available regarding the use of azilsartan medoxomil during breastfeeding, Azilsartan Medoxomil is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility

No data are available on the effect of azilsartan medoxomil on human fertility. Nonclinical studies demonstrated that azilsartan did not appear to affect male or female fertility in the rat.

4.7 Effects On Ability To Drive And Use Machines

Azilsartan medoxomil has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable Effects

Summary of the safety profile

Azilsartan Medoxomil at doses of 20, 40 or 80 mg has been evaluated for safety in clinical studies in patients treated for up to 56 weeks. In these clinical studies, adverse reactions associated with treatment with Azilsartan Medoxomil were mostly mild or moderate, with an overall incidence similar to placebo. The most common adverse reaction was dizziness. The incidence of adverse reactions with this treatment was not affected by gender, age, or race. Adverse reactions were reported at a similar frequency for the Azilsartan Medoxomil20 mg dose as with the 40 and 80 mg doses in one placebo controlled study.

Tabulated list of adverse reactions

Adverse reactions based on pooled data (40 and 80 mg doses) are listed below according to system organ class and preferred terms. These are ranked by frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Dizziness
Vascular disorders	Uncommon	Hypotension
Gastrointestinal disorders	Common Uncommon	Diarrhoea Nausea
Skin and subcutaneous tissue disorders	Uncommon Rare	Rash, pruritus Angioedema
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
General disorders and administration site conditions	Uncommon	Fatigue Peripheral oedema
Investigations	Common Uncommon	Blood creatine phosphokinase increased Blood creatinine increased Blood uric acid increased / Hyperuricemia

Description of selected adverse reactions

When Azilsartan Medoxomil was coadministered with chlortalidone, the frequencies of blood creatinine increased and hypotension were increased from uncommon to common.

When Azilsartan Medoxomil was coadministered with amlodipine, the frequency of peripheral oedema was increased from uncommon to common, but was lower than amlodipine alone.

Investigations

Serum creatinine

The incidence of elevations in serum creatinine following treatment with Azilsartan Medoxomil was similar to placebo in the randomised placebo-controlled monotherapy studies. Coadministration of Azilsartan Medoxomil with diuretics, such as chlortalidone, resulted in a greater incidence of creatinine elevations, an observation consistent with that of other angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors. The elevations in serum creatinine during coadministration of Azilsartan Medoxomil with diuretics were associated with larger blood pressure reductions compared with a single medicinal product. Many of these elevations were transient or no progressive while subjects continued to receive treatment. Following discontinuation of treatment, the majority of the elevations that had not resolved during treatment were reversible, with the creatinine levels of most subjects returning to baseline or near-baseline values.

Uric acid

Small mean increases of serum uric acid were observed with Azilsartan Medoxomil (10.8 µmol/l) compared with placebo (4.3 µmol/l).

Haemoglobin and haematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 3 g/l and 1 volume percent, respectively) were observed in placebo-controlled monotherapy studies. This effect is also seen with other inhibitors of the RAAS.

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

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. During controlled clinical studies in healthy subjects, once daily doses up to 320 mg of azilsartan medoxomil were administered for 7 days and were well tolerated.

Management

If symptomatic hypotension should occur, supportive treatment should be instituted and vital signs monitored.

Azilsartan is not removed by dialysis.

5. Pharmacological Properties

5.1 Mechanism of action

Azilsartan medoxomil is an orally active prodrug that is rapidly converted to the active moiety, azilsartan, which selectively antagonises the effects of angiotensin II by blocking its binding to the AT_1 receptor in multiple tissues. Angiotensin II is the principal pressor agent of the RAAS, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Blockade of the AT_1 receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increases in plasma renin activity and angiotensin II circulating levels do not overcome the antihypertensive effect of azilsartan.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, plain, ATC Code: C09CA09

Essential hypertension

In seven double blind controlled studies, a total of 5,941 patients (3,672 given Azilsartan Medoxomil, 801 given placebo, and 1,468 given active comparator) were evaluated. Overall, 51% of patients were male and 26% were 65 years or older (5% ≥ 75 years); 67% were white and 19% were black.

Azilsartan Medoxomil was compared with placebo and active comparators in two 6 week randomised, double blind studies. Blood pressure reductions compared with placebo based on 24-hour mean blood pressure by ambulatory blood pressure monitoring (ABPM) and clinic blood pressure measurements at trough are shown in the table below for both studies. Additionally, Azilsartan Medoxomil80 mg resulted in significantly greater reductions in SBP than the highest approved doses of olmesartan medoxomil and valsartan.

	Placebo	**Azilsartan Medoxomil20 mg**	**Azilsartan Medoxomil40mg #**	**Azilsartan Medoxomil80mg #**	**OLM-M 40mg #**	**Valsartan 320mg#**
Primary end point: **24 Hour Mean SBP: LS Mean Change from Baseline (BL) to Week 6 (mm Hg)**						
Study 1						
Change from BL	-1.4	-12.2 *	-13.5 *	-14.6 *†	-12.6	-
Study 2						
Change from BL	-0.3	-	-13.4 *	-14.5 *†	-12.0	-10.2

Key Secondary End Point: **Clinic SBP: LS Mean Change from Baseline (BL) to Week 6 (mm Hg) (LOCF)**						
Study 1						
Change from BL	-2.1	-14.3 *	-14.5 *	-17.6 *	-14.9	-
Study 2						
Change from BL	-1.8	-	-16.4 *†	-16.7 *†	-13.2	-11.3
OLM-M = olmesartan medoxomil, LS = least squares, LOCF = last observation carried forward * Significant difference vs. Placebo at 0.05 level within the framework of the step-wise analysis † Significant difference vs. Comparator(s) at 0.05 level within the framework of the step-wise analysis # Maximum dose achieved in study 2. Doses were force-titrated at Week 2 from 20 to 40 mg and 40 to 80 mg for Azilsartan Medoxomil, and 20 to 40 mg and 160 to 320 mg, respectively, for olmesartan medoxomil and valsartan						

In these two studies, clinically important and most common adverse events included dizziness, headache and dyslipidemia. For Azilsartan Medoxomil, olmesartan medoxomil and valsartan, respectively dizziness was observed at an incidence of 3.0%, 3.3% and 1.8%; headache at 4.8%, 5.5% and 7.6% and dyslipidemia at 3.5%, 2.4% and 1.1%.

In active-comparator studies with either valsartan or ramipril, the blood-pressure-lowering effect with Azilsartan Medoxomil was sustained during long-term treatment. Azilsartan Medoxomil had a lower incidence of cough (1.2%) compared with ramipril (8.2%).

The antihypertensive effect of azilsartan medoxomil occurred within the first 2 weeks of dosing with the full effect achieved by 4 weeks. The blood pressure lowering effect of azilsartan medoxomil was also maintained throughout the 24 hour dosing interval. The placebo-corrected trough-to-peak ratios for SBP and DBP were approximately 80% or higher.

Rebound hypertension was not observed following abrupt cessation of Azilsartan Medoxomil therapy after 6 months of treatment.

No overall differences in safety and effectiveness were observed between elderly patients and younger patients, but greater sensitivity to blood pressure lowering effects in some elderly individuals cannot be ruled out. As with other angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors the antihypertensive effect was lower in black patients (usually a low-renin population).

Co-administration of Azilsartan Medoxomil 40 and 80 mg with a calcium channel blocker (amlodipine) or a thiazide-type diuretic (chlortalidone) resulted in additional blood pressure reductions compared with the other antihypertensive alone. Dose dependent adverse events

including dizziness, hypotension and serum creatinine elevations were more frequent with diuretic coadministration compared with Azilsartan Medoxomilalone, while hypokalemia was less frequent compared with diuretic alone.

Beneficial effects of Azilsartan Medoxomil on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Effect on cardiac repolarisation

A thorough QT/QTc study was conducted to assess the potential of azilsartan medoxomil 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 medoxomil.

Additional information

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

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Azilsartan Medoxomil in one or more subsets of the paediatric population in hypertension.

5.3 Pharmacokinetic properties

Following oral administration, azilsartan medoxomil is rapidly hydrolyzed to the active moiety azilsartan in the gastrointestinal tract and/or during absorption. Based on *in vitro* studies, carboxymethylenebutenolidase is involved in the hydrolysis in the intestine and liver. In addition, plasma esterases are involved in the hydrolysis of azilsartan medoxomil to azilsartan.

Absorption

The estimated absolute oral bioavailability of azilsartan medoxomil based on plasma levels of azilsartan is approximately 60%. After oral administration of azilsartan medoxomil, peak plasma concentrations (C_{max}) 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 16 litres. Azilsartan is highly bound to plasma proteins (> 99%), mainly serum albumin. Protein binding is constant at azilsartan plasma concentrations well above the range achieved with recommended doses.

Biotransformation

Azilsartan is metabolised 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% that of azilsartan, respectively. M-I and M-II do not contribute to the pharmacologic activity of azilsartan medoxomil. The major enzyme responsible for azilsartan metabolism is CYP2C9.

Elimination

Following an oral dose of ^{14}C-labelled azilsartan medoxomil, approximately 55% of radioactivity was recovered in faeces 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.

Linearity/non-linearity

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.

Characteristics in specific groups of patients

Paediatric population

The pharmacokinetics of azilsartan have not been studied in children under 18 years of age.

Older people

Pharmacokinetics of azilsartan do not differ significantly between young (age range 18-45 years) and elderly (age range 65-85 years) patients.

Renal impairment

In patients with mild, moderate, and severe renal impairment azilsartan total exposure (AUC) was +30%, +25% and +95% increased. No increase (+5%) was observed in end-stage renal disease patients who were dialysed. However, there is no clinical experience in patients with severe renal impairment or end stage renal disease. Hemodialysis does not remove azilsartan from the systemic circulation.

Hepatic impairment

Administration of Azilsartan Medoxomil for up to 5 days in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment resulted in slight increase in azilsartan exposure (AUC increased by 1.3 to 1.6 fold). Azilsartan Medoxomilhas not been studied in patients with severe hepatic impairment.

Gender

Pharmacokinetics of azilsartan do not differ significantly between males and females. No dose adjustment is necessary based on gender.

Race

Pharmacokinetics of azilsartan do not differ significantly between black and white populations. No dose adjustment is necessary based on race.

6. Nonclinical safety data

6.1 Animal Toxicology or Pharmacology

In preclinical safety studies, azilsartan medoxomil and M-II, the major human metabolite, were examined for repeated-dose toxicity, reproduction toxicity, mutagenicity and carcinogenicity.

In the repeated-dose toxicity studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters, changes in the kidney and renal haemodynamics, as well as increased serum potassium in normotensive animals. These effects, which were prevented by oral saline supplementation, do not have clinical significance in treatment of hypertension.

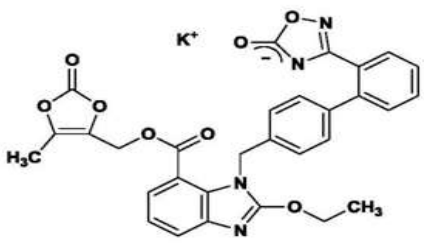
In rats and dogs, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

Azilsartan and M-II crossed the placenta and were found in the fetuses of pregnant rats and were excreted into the milk of lactating rats. In the reproduction toxicity studies, there were no effects on male or female fertility. There is no evidence of a teratogenic effect, but animal studies indicated some hazardous potential to the postnatal development of the offspring such as lower body weight, a slight delay in physical development (delayed incisor eruption, pinna detachment, eye opening), and higher mortality.

Azilsartan and M-II showed no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice.

7. Description

The potassium salt of azilsartan medoxomil, azilsartan kamedoxomil, is chemically described as (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4oxadiazol-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:



ZILSAR 40

Azilsartan Medoxomil Tablets are white to off-white, circular, biconvex uncoated tablets with break line on one side.

ZILSAR 80

Azilsartan Medoxomil Tablets are white to off-white, circular, biconvex uncoated tablets.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 **Shelf-Life**

Do not use later than date of expiry.

8.3 Packaging Information

ZILSAR is available in Blister strip of 10 Tablets

8.4 Storage and Handing Instructions

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

Keep out of reach of children.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What ZILSAR is and what it is used for

ZILSAR contains an active substance called azilsartan medoxomil and belongs to a class of medicines called angiotensin II receptor antagonists (AIIRAs). Angiotensin II is a substance which occurs naturally in the body and which causes the blood vessels to tighten, therefore increasing your blood pressure. ZILSAR blocks this effect so that the blood vessels relax, which helps lower your blood pressure.

Azilsartan is indicated for the treatment of hypertension in adult patient, either alone or in combination with other antihypertensive agents.

9.2.What you need to know before you take ZILSAR

Do NOT take ZILSAR if you

- are allergic to azilsartan medoxomil or any of the other ingredients of this medicine.

- are more than 3 months pregnant. (It is also better to avoid this medicine in early pregnancy - see pregnancy section).

- have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking ZILSAR, especially if you

- have kidney problems.

- are on dialysis or had a recent kidney transplant.

- have severe liver disease.

- have heart problems (including heart failure, recent heart attack).

- have ever had a stroke.

- have low blood pressure or feel dizzy or lightheaded.

- are vomiting, have recently had severe vomiting, or have diarrhoea. - have raised levels of potassium in your blood (as shown in blood tests).

- have a disease of the adrenal gland called primary hyperaldosteronism.

- have been told that you have a narrowing of the valves in your heart (called “aortic or mitral valve stenosis”) or that the thickness of your heart muscle is abnormally increased (called “obstructive hypertrophic cardiomyopathy”).

- are taking any of the following medicines used to treat high blood pressure:

- An ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
- Aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take ZILSAR”.

You must tell your doctor if you think you are (or might become) pregnant. ZILSAR is not recommended in early pregnancy, and must NOT be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see section "Pregnancy section and breastfeeding"). ZILSAR may be less effective in lowering the blood pressure in black patients.

Children and adolescents

There is limited data on the use of ZILSAR in children or adolescents under 18 years of age. Therefore, this medicine should not be given to children or adolescents.

Other medicines and ZILSAR

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

ZILSAR can affect the way some other medicines work and some medicines can have an effect on ZILSAR.

In particular, tell your doctor if you are taking any of the following medicines:

- Lithium (a medicine for mental health problems)

- Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac or celecoxib (medicines to relieve pain and inflammation)

- Acetylsalicylic acid if taking more than 3 g per day (medicine to relieve pain and inflammation)

- Medicines that increase the amount of potassium in your blood; these include potassium supplements, potassium-sparing medicines (certain 'water tablets') or salt substitutes containing potassium

- Heparin (a medicine for thinning the blood)

- Diuretics (water tablets)

- Aliskiren or other medicines to lower your blood pressure (angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, such as enalapril, lisinopril, ramipril or valsartan, telmisartan, Irbesartan).

Your doctor may need to change your dose and/or to take other precautions if you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take ZILSAR" and "Warnings and precautions").

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking this medicine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of ZILSAR.

ZILSAR is not recommended in early pregnancy, and must NOT be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding. ZILSAR is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

ZILSAR is unlikely to have an effect on driving or using machines. However some people may feel tired or dizzy when taking this medicine and if this happens to you, do not drive or use any tools or machines.

9.3.How to take ZILSAR

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. It is important to keep taking ZILSAR every day at the same

time. ZILSAR is for oral use. Take the tablet with plenty of water. You can take this medicine with or without food.

- The usual starting dose is 40 mg once a day. Your doctor may increase this dose to a maximum of 80 mg once a day depending on blood pressure response.

- For patients such as the very elderly (75 years and above) your doctor may recommend a lower starting dose of 20 mg once a day.

- If you suffer from mild or moderate liver disease your doctor may recommend a lower starting dose of 20 mg once a day.

- For patients who recently have lost body fluids e.g. through vomiting or diarrhoea, or by taking water tablets, your doctor may recommend a lower starting dose of 20 mg once a day.

- If you suffer from other coexisting illnesses such as severe kidney disease or heart failure your doctor will decide on the most appropriate starting dose.

If you take more ZILSAR than you should

If you take too many tablets, or if someone else takes your medicine, contact your doctor immediately. You may feel faint or dizzy if you have taken more than you should.

If you forget to take ZILSAR

Do not take a double dose to make up for a forgotten dose. Just take the next dose at the usual time.

If you stop taking ZILSAR

If you stop taking ZILSAR, your blood pressure may increase again. Therefore do not stop taking ZILSAR without first talking to your doctor about alternative treatment options.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4.Possible side effects

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

Stop taking ZILSAR and seek medical help immediately if you have any of the following allergic reactions, which occur rarely (may affect up to 1 in 1,000 people):

- Difficulties in breathing, or swallowing, or swelling of the face, lips, tongue and/or throat (angioedema)

- Itching of the skin with raised lumps.

Other possible side effects include:

Common side effects (may affect up to 1 in 10 people):

- Dizziness

- Diarrhoea

- Increased blood creatine phosphokinase (an indicator of muscle damage).

Uncommon side effects (may affect up to 1 in 100 people):

- Low blood pressure, which may make you feel faint or dizzy

- Feeling tired

- Swelling of the hands, ankles or feet (peripheral oedema)

- Skin rash and itching

- Nausea

- Muscle spasms

- Increased serum creatinine in the blood (an indicator of kidney function)

- Increased uric acid in the blood.

Rare side effects (may affect up to 1 in 1,000 people):

- Changes in blood test results including decreased levels of a protein in the red blood cells (haemoglobin).

When ZILSAR is taken with chlortalidone (a water tablet), higher levels of certain chemicals in the blood (such as creatinine), which are indicators of kidney function, have been seen commonly (in less than 1 in 10 users), and low blood pressure is also common.

Swelling of the hands, ankles or feet is more common (in less than 1 in 10 users) when ZILSAR is taken with amlodipine (a calcium channel blocker for treating hypertension) than when ZILSAR is taken alone (less than 1 in 100 users). The frequency of this effect is highest when amlodipine is taken alone.

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

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

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of the month.

Store ZILSAR in the original package in order to protect it from light and moisture. This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6.Contents of the pack and other information

What ZILSAR contains

- The active substance is azilsartan medoxomil (as potassium).

ZILSAR 40: Each tablet contains 40 mg azilsartan medoxomil

ZILSAR 80: Each tablet contains 80 mg azilsartan medoxomil

10. DETAILS OF MANUFACTURE

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 17.12.2016

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ZILSAR 40, 80 MG/AUg-20/01/PI