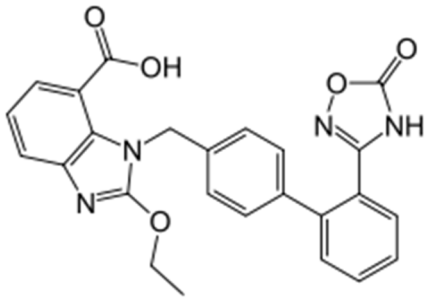
To be sold by retail on the prescription of Cardiologist only

EDDZAAR 40/EDDZAAR 80
(Azilsartan medoxomil Tablets 40/ 80)

COMPOSITION
Each film coated tablet contains:
Azilsartan Medoxomil…… 40 mg/80 mg
Excipients……... q.s.
Colours: Quinoline Yellow Lake & Titanium Dioxide I.P.

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.
The drug substance used in the drug product formulation is the potassium salt of azilsartan medoxomil, also known by the US accepted name of azilsartan kamedoxomil and 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 $C_{30}H_{23}KN_4O_8$ and its structural formula is:



Azilsartan kamedoxomil is a white to nearly white powder with a molecular weight of 606.62. It is practically insoluble in water and freely soluble in methanol.

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

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 alone, additional blood pressure reduction can be achieved when Azilsartan is coadministered with other antihypertensive medicinal products, including diuretics (such as chlortalidone and hydrochlorothiazide) and calcium channel blockers.

Special populations

Older people (65 years and over)

No initial dose adjustment with Azilsartan 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 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 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 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 should be initiated under close medical supervision and consideration can be given to 20 mg as a starting dose.

Heart failure

Caution should be exercised in hypertensive patients with congestive heart failure as there is no experience of use of Azilsartan in these patients.

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 and concomitant therapy may be needed more frequently for blood pressure control in black patients.

Paediatric population

The safety and efficacy of Azilsartan in children and adolescents 0 to < 18 years have not yet been established.

No data are available.

Method of administration

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

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimester of pregnancy.
- The concomitant use of Azilsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Activated renin-angiotensin-aldosterone system

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

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 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 renin-angiotensin-aldosterone system (RAAS)

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

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 in patients who have recently undergone kidney transplantation.

Hepatic impairment

Azilsartan 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. Hypovolemia should be corrected prior to administration of Azilsartan, 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 renin-angiotensin system. Therefore, the use of Azilsartan is not recommended in these patients.

Hyperkalaemia

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of Azilsartan 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 is not recommended.

DRUG-INTERACTION
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 renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension,

hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
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.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

There are no data from the use of Azilsartan 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, 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.

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

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacodynamics properties it is expected that azilsartan medoxomil would have negligible influence on the ability to drive and use machines. However, when taking any antihypertensive it should be taken into account that occasionally dizziness or tiredness may occur.

UNDESIRABLE EFFECTS

Summary of the safety profile

Azilsartan 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 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 Azilsartan was not affected by gender, age, or race.

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Adverse reactions were reported at a similar frequency for the Azilsartan 20 mg dose as with the 40 and 80 mg doses in one placebo controlled study.

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

When Azilsartan 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 was similar to placebo in the randomised placebo-controlled monotherapy studies. Coadministration of Azilsartan 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 with diuretics were associated with larger blood pressure reductions compared with a single medicinal product. Many of these elevations were transient or nonprogressive 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 (10.8 µmol/l) compared with placebo (4.3 µmol/l).

Hemoglobin and hematocrit
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 renin-angiotensin-aldosterone system.

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 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain
ATC Code: C09CA09
Mechanism of action and pharmacodynamics effect
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 renin-angiotensin system, 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.

Essential hypertension
In seven double blind controlled studies, a total of 5941 patients (3672 given Azilsartan, 801 given placebo, and 1468 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 was compared with placebo and active comparators in two 6-week randomized, 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

80 mg resulted in significantly greater reductions in SBP than the highest approved doses of olmesartan medoxomil and valsartan.

	Placebo	**Azilsartan 20 mg**	**Azilsartan 40 mg#**	**Azilsartan 80 mg#**	**OLM-M 40 mg#**	**Valsartan 320 mg#**
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, 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, 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 was sustained during long-term treatment. Azilsartan had a lower incidence of cough (1.2%) compared with ramipril (8.2%).

The antihypertensive effect of Azilsartan occurred within the first 2 weeks of dosing with the full effect achieved by 4 weeks. The blood pressure lowering effect of Azilsartan 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 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).
Coadministration of Azilsartan 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 alone, while hypokalemia was less frequent compared with diuretic alone.
Beneficial effects of Azilsartan 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 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.
Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Azilsartan in one or more subsets of the paediatric population in hypertension.

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 pharmacodynamics 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.

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. 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 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.

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 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 has 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.

PRECLINICAL SAFETY DATA
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 haemodynamic, 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 foetuses 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.

EXPIRY DATE
Do not use later than the Use before date.

PACKAGING INFORMATION
Alu -Alu Blister of 10 Tablets

STORAGE AND HANDLING INSTRUCTIONS
Store protected from light and moisture at a temperature not exceeding 25 ºC

MARKETED BY
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