SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished product:

ADARBI 40 TABLET (Azilsartan Medoxomil Tablet40 mg)

2. Qualitative and Quantitative composition:

COMPOSITION:

Each Film coated tablet contains:
Azilsartan Kamedoxomil
Eq. to Azilsartan Medoxomil ..… 40 mg
Excipients..... q.s.

1.	Azilsartan Kamedoxomil
2.	Mannitol
3.	Povidone K 30
4.	Microcrystalline Cellulose
5.	Methylene Chloride
6.	Magnesium Stearate
7.	Croscarmellose Sodium
8.	Opadry 03k19229 Clear
9.	Opadry Clear OY-S-29038 (Vaniila Flavour)
10.	Ethanol 96%

.

3. Pharmaceutical Form: Film coated tablet

4. Clinical Particulars:

4.1 Therapeutic Indications:
Adarbi (Azilsartan Medoxomil) is indicated for the treatment of hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily stroke and myocardial infarction. Adarbi (Azilsartan Medoxomil) may be used either alone or in combination with other antihypertensive agents.

4.2 Posology and method of administration:
The recommended dose in adults is 80 mg taken orally once daily. Consider a Starting dose of 40 mg for patients who are treated with high doses of diuretics.
If blood pressure is not controlled with Adarbi alone, additional blood pressure reduction can be achieved by taking Adarbi with other antihypertensive agents.

4.3 Contraindications
It is contraindicated to co-administer Aliskiren with Azilsartan in patients with Diabetes.
Hypersensitivity to the active substance or to any of the excipients used. Second and third trimester of pregnancy

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 ADARBI.
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 ADARBI 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 ADARBI in patients who have recently undergone kidney transplantation.

Hepatic impairment

ADARBI 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 ADARBI. Hypovolemia should be corrected prior to administration of ADARBI, 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 ADARBI is not recommended in these patients.

Hyperkalaemia

Based on experience with the use of other medicinal products that affect the RAAS, concomitant use of ADARBI 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 ADARBI is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No 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. The antihypertensive effect of Azilsartan may be attenuated by the non-steroidal anti-inflammatory drugs including selective COX-2 inhibitors. Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors or aliskiren is associated with increased risks of hypotension, hyperkalemia and changes in renal function.

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 Pregnancy and Lactation:

Pregnancy Category D. The risk to the fetus increases if Azilsartan Medoxomil is administered during the second or third trimesters of pregnancy. It is not known whether Azilsartan Medoxomil is excreted in human milk, as many drugs are excreted in human milk and 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.

4.7 Effects on the 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

ADARBI 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 ADARBI 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 ADARBI 20 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 ADARBI was coadministered with chlortalidone, the frequencies of blood creatinine increased and hypotension were increased from uncommon to common.

When ADARBI 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 ADARBI was similar to placebo in the randomised placebo-controlled monotherapy studies. Coadministration of ADARBI 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 coadminstiration of ADARBI 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 ADARBI (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 RAAS.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product.

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 Particulars:

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists

ATC code: C09CA09

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.
Essential hypertension
In seven double blind controlled studies, a total of 5,941 patients (3,672 given ADARBI, 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.
ADARBI 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, ADARBI 80 mg resulted in significantly greater reductions in SBP than the highest approved doses of olmesartan medoxomil and valsartan.

	Placebo	**ADARBI 20 mg**	**ADARBI 40mg#**	**ADARBI 80mg#**	**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 ADARBI, 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 ADARBI, 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 ADARBI was sustained during long-term treatment. ADARBI 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 ADARBI 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 ADARBI 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 ADARBI alone, while hypokalemia was less frequent compared with diuretic alone.
Beneficial effects of ADARBI 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 ADARBI in one or more subsets of the paediatric population in hypertension.

5.2 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 ADARBI 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). ADARBI 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.

5.3 Pre-clinical Safety:
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.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Mannitol	BP
Povidone K 30	BP
Microcrystalline Cellulose	BP
Methylene Chloride	BP
Magnesium Stearate	BP
Croscarmellose Sodium	BP
Opadry 03k19229 Clear	IH
Opadry Clear OY-S-29038 (Vaniila Flavour)	IH
Ethanol 96%	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: 24 months

6.4 Special Precautions for storage:
Don't store above 30^{o}C. Keep out of the sight and reach of children.

6.5 Nature and contents of container:

2 Alu-Alu Blisters of 10 tablets each packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling
None

7. Marketing Authorization Holder:
NIPRO JMI Pharma Ltd.

8. Marketing Authorization Number:

06457/07133/NMR/2018

9. Date of first Authorization /renewal of the authorization:
Aug 5, 2021

10. Date of revision of text:
May 2018