SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Edarbi 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Edarbi 20 mg tablets

Each tablet contains 20 mg of azilsartan medoxomil (as potassium).

3 PHARMACEUTICAL FORM

Tablet.

Edarbi 20 mg tablets

White to nearly white round tablets, 6.0 mm in diameter, debossed “ASL” on one side and “20” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Edarbi is indicated for the treatment of essential hypertension in adults.

4.2 Posology and method of administration

Posology

The recommended starting dose in adults 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 Edarbi alone, 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 (see sections 4.3, 4.4, 4.5 and 5.1).

Special populations

Elderly (65 years and over)
No initial dose adjustment with Edarbi is necessary in elderly patients (see section 5.2), 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 Edarbi in these patients (see sections 4.4 and 5.2). Haemodialysis does not remove azilsartan from the systemic circulation.
No dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment
Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group (see sections 4.4 and 5.2).
As there is limited experience of use of Edarbi in patients with mild to moderate hepatic impairment close monitoring is recommended and consideration should be given to 20 mg as a starting dose (see section 5.2).

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), Edarbi should be initiated under close medical supervision and consideration can be given to 20 mg as a starting dose (see section 4.4).

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 (see section 5.1). This generally has been true for other angiotensin II receptor (AT_1) antagonists and angiotensin-converting enzyme inhibitors. Consequently, uptitration of Edarbi and concomitant therapy may be needed more frequently for blood pressure control in black patients.

Paediatric population
Edarbi is not indicated for use in children or adolescents under 18 years of age. Currently available data in children or adolescents 6 to < 18 years of age are described

in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made. The safety and efficacy of Edarbi in children < 6 years of age have not yet been established.
No data are available.

Method of administration

Edarbi is for oral use and may be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Edarbi with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see sections 4.5 and 5.1).

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 Edarbi.

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 Edarbi in these patients (see sections 4.2 and 5.2).

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 (see sections 4.5 and 5.1).
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 Edarbi in patients who have recently undergone kidney transplantation.

Hepatic impairment
Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group (see sections 4.2 and 5.2).

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

Hyperkalaemia
Based on experience with the use of other medicinal products that affect the RAAS, concomitant use of Edarbi 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 (see section 4.5). 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).

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, azilsartan medoxomil should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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 (see sections 4.3 and 4.6).

Lithium
As with other angiotensin II receptor antagonists the combination of lithium and Edarbi is not recommended (see section 4.5).

Edarbi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of 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 (see section 4.4).

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 (see sections 4.3, 4.4 and 5.1).

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. Following administration with a mixture of cytochrome P450 (CYP) probe substrates, no

clinically significant drug interactions were observed with caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), or midazolam (CYP3A4).

Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastrointestinal tract and/or during drug absorption (see section 5.2). *In vitro* studies indicated that interactions based on esterase inhibition are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4).
The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

There are no data from the use of azilsartan medoxomil in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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) (see section 5.3).

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 (see sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the use of azilsartan medoxomil during breastfeeding, Edarbi 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 (see section 5.3).

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

Edarbi at doses of 20, 40 or 80 mg has been evaluated for safety in clinical studies in adult patients treated for up to 56 weeks. In these clinical studies, adverse reactions associated with treatment with Edarbi 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 Edarbi 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse drug reactions from clinical trials and post marketing experience		
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	Not known Uncommon	Arthralgia Muscle spasms
General disorders and administration site conditions	Uncommon	Fatigue Peripheral oedema
Investigations	Common Uncommon	Blood creatine phosphokinase increased

Adverse drug reactions from clinical trials and post marketing experience		
System organ class	**Frequency**	**Adverse reaction**
		Blood creatinine increased Blood uric acid increased / Hyperuricemia

Description of selected adverse reactions
When Edarbi was coadministered with chlortalidone, the frequencies of blood creatinine increased and hypotension were increased from uncommon to common.

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

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor
antagonists (see section 4.4).

Investigations

Serum creatinine
The incidence of elevations in serum creatinine following treatment with Edarbi was similar to placebo in the randomised placebo-controlled monotherapy studies. Coadministration of Edarbi 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 Edarbi 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 Edarbi (10.8 µmol/L) compared with placebo (4.3 µmol/L).

Haemoglobin and haematocrit
Small decreases in haemoglobin and haematocrit (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.

Paediatric population
A clinical study on the safety and efficacy of Edarbi in children and adolescents 6 to < 18 years of age was conducted (see section 5.1*)*. The overall safety profile of Edarbi in the paediatric population was consistent with the known safety profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 adult 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 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, plain, 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 (see section 5.2). 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 adult patients (3 672 given Edarbi, 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.

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

	Placebo	**Edarbi 20 mg**	**Edarbi 40 mg#**	**Edarbi 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 Edarbi, 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 Edarbi, 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 Edarbi was sustained during long-term treatment. Edarbi 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 Edarbi 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 (see section 4.2). 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 Edarbi 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 Edarbi alone, while hypokalemia was less frequent compared with diuretic alone.

Beneficial effects of Edarbi 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 antihypertensive effects of azilsartan medoxomil were evaluated in a Phase 3 randomised, double-blind study in children or adolescents 6 to < 18 years of age with primary or secondary hypertension. This study involved a 6-week, double-blind, randomised treatment phase (DB Phase), followed by a 2-week, double-blind, randomised placebo-controlled withdrawal phase (WD Phase). In the DB Phase, subjects were randomised (1:1:1:1) to the following groups: azilsartan medoxomil 10 mg, 20 mg, and 40 mg/80 mg (based on subject body weight), or losartan. All patients started at the 10 mg treatment for 2 weeks; subsequently, patients either continued at 10 mg or were up-titrated to 20, 40, or 80 mg. In the WD Phase, subjects were randomised (1:1) to continue taking their previously assigned active treatment or were switched to placebo. This study also included a 44-week, open-label extension (OL Phase), in which all subjects received azilsartan medoxomil or azilsartan medoxomil and other antihypertensive medications as needed in a titrate-to-target blood pressure dosing algorithm, starting at 10 mg azilsartan medoxomil.

In the 6-week DB Phase, 162 subjects were exposed to azilsartan medoxomil. In the 2-week WD Phase, 77 subjects were exposed to azilsartan medoxomil and 103 subjects were exposed to placebo. In the 44-week OL Phase, 156 subjects were exposed to azilsartan medoxomil alone and 41 subjects were exposed to azilsartan medoxomil and other antihypertensives.

In the 2-week withdrawal period, there was a loss of blood pressure control in subjects randomised to placebo, while subjects who remained on azilsartan medoxomil treatment had stable blood pressure control. The difference in mean seated diastolic blood pressure change from Week 6 to Week 8 in the subjects treated with azilsartan medoxomil versus placebo was -5.42 mmHg (95% CI, -7.29 to -3.55 mmHg; $p < 0.001$). Percentage of subjects who achieved target blood pressure (defined as $< 90^{th}$ percentile for age, gender, and height) at Week 8 (week 2 of the withdrawal period) was significantly higher with azilsartan medoxomil treatment compared with placebo. Subjects who were treated with azilsartan medoxomil (all doses pooled) had a statistically significantly greater change in mean seated DBP from baseline to Week 6 compared with losartan-treated subjects. The effect of azilsartan medoxomil remained consistent over time during the open-label phase.

5.2 Pharmacokinetic properties

Following oral administration, azilsartan medoxomil is rapidly hydrolysed 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 (see section 4.2).

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 population pharmacokinetics of azilsartan following oral doses of azilsartan medoxomil were evaluated in hypertensive children aged 6 to < 18 years in a single dose study as well as in a multiple dose study of 10 mg to a maximum of 80 mg for 6 weeks. Generally, a dose proportional increase of the maximum concentration ($C_{max,ss}$) and exposure (AUC_{ss}) of azilsartan was observed. Exposure of azilsartan was dependent on body weight, generally a higher exposure was observed for paediatric patients weighing ≤ 50 kg compared to those weighing > 50 kg. The azilsartan exposure was similar between children and adults when allometric scaling was applied.

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 (see section 4.2). Haemodialysis does not remove azilsartan from the systemic circulation.

Hepatic impairment
Administration of Edarbi 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, see section 4.2). Edarbi 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 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 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.

Juvenile animal studies
Juvenile oral toxicity studies up to 3 months in duration in rats (2 or 3 weeks old) with azilsartan medoxomil, alone or in combination with M-II, showed that juvenile rats may be more susceptible to angiotensin-related altered renal morphology and function when exposed from postnatal week 2, corresponding with the period of growth and maturation of the renal system. The growth and maturation stage of the human renal system extends to about 2 years of age.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Fumaric acid (E 297)
Sodium hydroxide
Hydroxypropylcellulose (E 463)
Croscarmellose sodium
Microcrystalline cellulose (E 460)
Magnesium stearate (E 572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium blisters

Pack sizes: 14, 28, 56 or 98 tablets.

or

Aluminium blisters integrated with desiccant

Pack sizes: 14, 28, 30, 56, 90 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15475/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

10/03/2025