SAMENVATTING VAN DE PRODUCTKENMERKEN

1. NAME OF THE MEDICINAL PRODUCT

Edarclor 40 mg/12,5 mg, filmomhulde tabletten
Edarclor 40 mg/25 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Edarclor 40 mg/12.5 mg film-coated tablets:
Each tablet contains 40 mg of azilsartan medoxomil (as potassium) and 12.5 mg chlortalidone.

Edarclor 40 mg/25 mg film-coated tablets:
Each tablet contains 40 mg of azilsartan medoxomil (as potassium) and 25 mg chlortalidone.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Edarclor 40 mg/12.5 mg film-coated tablets:
Pale red, round, (approximately 9.7 mm in diameter), biconvex, film-coated tablet with A/C 40/12.5 on one side.

Edarclor 40 mg/25 mg film-coated tablets:
Light red, round, (approximately 9.7 mm in diameter), biconvex, film coated tablet with A/C 40/25 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension in adults.

Edarclor is a fixed-dose combination indicated in adults whose blood pressure is not adequately controlled by azilsartan medoxomil monotherapy.

4.2 Posology and method of administration

Posology

Adults
The recommended starting dose is 40 mg/12.5 mg once daily in patients whose blood pressure is not adequately controlled with current antihypertensive monotherapy such as Edarbi 40 mg or Edarbi 80 mg.

If needed the dose may be increased to a maximum of 40 mg/25 mg once daily.
Near-maximal antihypertensive effect is usually evident within 1-2 weeks of dosing, with maximal effects attained by 4 weeks.

Special populations

Older people (65 years and over)
No initial dose adjustment with Edarclor is necessary in elderly patients; caution should be exercised and close medical monitoring is recommended in the very elderly (≥ 75 years), who may be at increased risk of adverse events (see section 5.2).

Renal impairment
Chlortalidone, a component drug of Edarclor, should not be used in patients with severe renal impairment (GFR <30 mL/min/1.73m^2) and anuria (see section 4.3). There is no experience regarding the administration of Edarclor in patients with recent kidney transplantation. No dose adjustment is required in patients with mild or moderate renal impairment (GFR ≥30-<90 mL/min/1.73m^2).

Hepatic impairment
Chlortalidone, a component drug of Edarclor, should not be used in patients with severe hepatic impairment (see section 4.3). There is limited experience of use of Edarclor in patients with mild to moderate hepatic impairment; however, no initial dose adjustment of Edarclor is necessary in patients with mild to moderate hepatic impairment.

Thiazides should be used with caution in patients with impaired hepatic function (see sections 4.3 and 4.4). Minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma. Close monitoring is recommended (see section 5.2).

Intravascular volume depletion
For patients with depletion of intravascular volume or salt (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics), Edarclor should be initiated under close medical supervision only after correct volume has been obtained (see section 4.4).

A transient hypotensive response due to volume depletion does not preclude patients from further treatment, which usually can be continued without difficulty once the blood pressure and volume status have stabilized.

Heart failure
Caution should be exercised in hypertensive patients with congestive heart failure as there is no experience of use of Edarclor in these patients (see section 4.4).

Black population
No dose adjustment is required in the black population, who are commonly characterised as “low renin” hypertensives with an attenuated response to Renin-Angiotensin-Aldosterone System (RAAS) blockers. The blood pressure effect and safety profile of Edarclor in black patients are similar to those in the non-black population.

Paediatric population
The safety and efficacy of Edarclor in children and adolescents aged 0 to <18 years have not been established. No data are available.

Method of administration
Edarclor 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.
- Pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment.
- Severe renal impairment (GFR <30 mL/min/1.73m^2).
- Anuria.
- Refractory hyponatraemia (see sections 4.4 and 4.8).

- Hypercalcaemia (see sections 4.4).
- Symptomatic hyperuricaemia (see sections 4.4 and 4.8).
- Concomitant use of Edarclor with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

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 (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.

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, or underlying renal disease, including bilateral renal artery stenosis), treatment with medicinal products that affect this system, such as ACE-inhibitors and angiotensin II receptor blockers, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with Edarclor.

Evaluation of hypertensive patients with activated RAAS should include periodic assessment of renal function and electrolyte levels.

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

Renal impairment
Chlortalidone, a component drug of Edarclor, should not be used in severe renal impairment (GFR <30 mL/min/1.73m^2) (see section 4.3). No dose adjustment is required in patients with mild or moderate renal impairment.

Observe for worsening renal function in patients with renal impairment by periodic monitoring of serum creatinine and electrolyte levels. Patients with renal impairment are more likely to report abnormally high serum creatinine values. In these patients, Edarclor should be carefully titrated with monitoring of blood pressure and renal function parameters. Renal function may worsen in patients with renal artery stenosis.

Chlortalidone should be used with caution in patients with renal impairment, since chlortalidone may precipitate azotaemia. If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

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

Hepatic impairment
Chlortalidone, a component drug of Edarclor, should not be used in severe hepatic impairment (see section 4.3).

There is limited experience of use of Edarclor in patients with mild to moderate hepatic impairment, however, based on PK data, no initial dose adjustment of Edarclor is necessary in patients with mild to

moderate hepatic impairment. Minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma. Close monitoring is therefore recommended (see section 5.2).

Hypotension in volume- and /or salt-depleted patients
For patients with possible depletion of intravascular volume or salt depletion (e.g. patients with vomiting, diarrhoea, or patients taking high doses of diuretics), Edarclor should be initiated under close medical supervision (see section 4.2). Volume- and/or salt- depletion should be corrected before initiating Edarclor treatment.

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 Edarclor is not recommended in these patients.

Electrolyte imbalance
As for any patient receiving diuretic therapy, determination of serum electrolytes should be performed periodically.

Thiazides can cause fluid or electrolyte imbalance (including hypokalaemia, hypercalcaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, asthenia, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see section 4.8). Fluid and electrolyte imbalance should be corrected prior to initiating treatment with Edarclor.

Hypokalaemia
Hypokalaemia is a dose-dependent adverse reaction that may develop with chlortalidone monotherapy. Concurrent therapy with azilsartan medoxomil has been shown to reduce chlortalidone-associated hypokalaemia. Coadministration of digitalis may exacerbate the adverse effects of hypokalaemia. Hypokalaemia should be corrected prior to initiating treatment with Edarclor.

Hyperkalaemia
Due to the antagonism of the angiotensin II receptors by the azilsartan medoxomil component of Edarclor, hyperkalaemia may occur. Although clinically significant hyperkalaemia has not been documented with Edarclor, risk factors for developing hyperkalaemia include renal impairment and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with Edarclor (see section 4.5).

Hyponatraemia and hypochloraemic alkalosis
Thiazides have been shown to induce hyponatraemia. Edarclor should not be used in patients with refractory hyponatraemia (see section 4.3). Chloride deficit is generally mild and usually does not require treatment.

Hypercalcaemia
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Edarclor should not be used in patients with hypercalcaemia (see section 4.3).

Hypomagnesaemia
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other agents causing vasodilation or volume depletion special caution is indicated in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance, so a dose adjustment of insulin or antidiabetic therapy may be required. Latent diabetes mellitus may become manifest during thiazide therapy. An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy.

Hyperuricaemia
Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving chlortalidone or other thiazide diuretics. Edarclor should not be used in patients with symptomatic hyperuricaemia (see section 4.3).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Pregnancy
Edarclor should not be used in pregnancy (see section 4.3).

Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Diuretics should not be used for the management of oedema or hypertension in pregnancy (see section 4.6).

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

Edarclor contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

Paediatric population
The safety and efficacy of Edarclor in children and adolescents aged 0 to <18 years have not been established. No data are available.

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 blockers. Lithium renal clearance is reduced by diuretics, such as chlortalidone, increasing the risk of lithium toxicity.

Due to the lack of experience with concomitant use of Edarclor and lithium, this combination is not recommended. If the combination proves necessary, consider monitoring of serum lithium levels when using Edarclor.

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 blockers 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, in patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function concomitant use of angiotensin II receptor blockers and NSAIDs may lead to an increased risk of worsening of renal function (including possible acute renal failure) and an increase in serum potassium. Therefore, adequate hydration and monitoring of renal function at the beginning of the treatment are recommended.

Potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
Based on experience with the use of other medicinal products that affect the RAAS, use of Edarclor with 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 4.4).

Digitalis
Coadministration of digitalis may exacerbate the adverse effects of hypokalemia (see section 4.4).

Additional information

Edarclor

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 (see sections 4.3, 4.4 and 5.1).

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

No drug interaction studies have been conducted with other drugs and Edarclor, although studies have been conducted with azilsartan medoxomil and chlortalidone.

Azilsartan medoxomil

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 a prodrug, which 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.

Chlortalidone

Diuretics potentiate the action of curare derivatives and antihypertensive agents (e.g. guanethidine, metyldopa, beta-blockers, vasodilators, calcium antagonists, ACE-inhibitors and ARBs).

The hypokalaemic effect of chlortalidone may be potentiated by corticosteroids, ACTH, β2-agonists, amphotericin and carbenoloxone.

Allopurinol
Coadministration of chlortalidone may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine
Chlortalidone may increase the risk of adverse effects caused by amantadine.

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of chlortalidone by decreasing gastrointestinal motility and stomach emptying rate.

Antidiabetic medicinal products (oral agents and insulin)
Dosage adjustment of the antidiabetic medicinal products may be required.

Calcium salts
The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if administered together with chlortalidone.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Colestyramine
Absorption of chlortalidone is impaired in the presence of anionic exchange resins. A decrease in the pharmacological effect may be expected.

Cytotoxic agents
Concurrent administration may reduce renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, metothrexate) and potentiate their myelosuppressive effects.

Diazoxide
The hyperglycaemic effect of diazoxide may be enhanced by chlortalidone.

4.6 Fertility, pregnancy and lactation

Pregnancy
Edarclor should not be used in pregnancy (see section 4.3 and 4.4).

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

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

Azilsartan medoxomil

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 blockers, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor blocker 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 blockers should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor blocker 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 blockers 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 blockers should be closely observed for hypotension (see sections 4.3 and 4.4).

Chlortalidone

Diuretics should not be used for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. Diuretics such as chlortalidone have been shown to cross the placental barrier and appear in cord blood. There have been reports of fetal bone marrow depression, thrombocytopenia, and fetal and neonatal jaundice associated with the use of thiazide-like diuretics.

Breastfeeding
No information is available regarding the use of Edarclor or azilsartan medoxomil during breastfeeding. However, chlortalidone passes into breast milk and Edarclor is therefore not recommended during breastfeeding. 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 Edarclor on human fertility. Nonclinical studies demonstrated that azilsartan medoxomil 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

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

4.8 Undesirable effects

Summary of the safety profile
Edarclor has been evaluated for safety in clinical studies in patients treated for up to 52 weeks. In these clinical studies, adverse reactions associated with treatment with Edarclor were mostly mild or moderate. The most common adverse reaction was blood creatinine increased. The increases in blood creatinine were dose-related and mostly transient or nonprogressive while on treatment, and reversible following cessation of treatment. The incidence of adverse reactions with Edarclor was not affected by gender, age, or race.

Clinical Investigation

In the short term studies, the safety profile was comparable to active comparators and showed no clinically important differences across diverse subgroups including age, gender, or race. When Edarclor was administered to patients not adequately controlled on azilsartan medoxomil 40 mg, the overall safety profile of Edarclor 40 mg/12.5 mg was similar to the safety profile of azilsartan medoxomil 40 mg. Edarclor 40 mg/25 mg was also safe and well tolerated, although elevated blood creatinine, headache and dizziness occurred more frequently in conjunction with greater blood pressure reduction. In the long term safety study in patients with moderate renal impairment, the adverse events observed were similar for Edarclor compared with olmesartan medoxomil/hydrochlorothiazide.

Cardiovascular outcome studies have shown that long-term treatment with chlortalidone reduces the risk of cardiovascular mortality and morbidity.

Tabulated list of adverse reactions
Adverse reactions based on pooled data from all Phase 3 clinical trials 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.

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Uncommon	Anaemia
Metabolism and nutrition disorders	Common	Blood uric acid increased, hyperuricaemia
	Uncommon	Hypokalaemia, blood potassium increased, hyponatraemia, blood sodium decreased, gout
Nervous system disorders	Common	Dizziness, dizziness postural
	Uncommon	Syncope, paraesthesia
Vascular disorders	Common	Hypotension
Gastrointestinal disorders	Common	Diarrhoea, nausea
	Uncommon	Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
General disorders and administration site conditions	Common	Fatigue
Investigations	Very common	Blood creatinine increased
	Common	Blood urea increased
	Uncommon	Blood glucose increased

Additional information on individual components

Adverse reactions known to occur with each component given singly but not seen in the clinical studies may occur during treatment with Edarclor.

Azilsartan medoxomil
In addition to the adverse reactions noted above for Edarclor, the following adverse reactions have been reported for azilsartan medoxomil:

Peripheral oedema, migraine, and increased blood creatine phosphokinase were reported as uncommon adverse reactions

Renal impairment was reported rarely during the clinical trials. Serious angioedema may occur rarely (≥ 1/10,000 to <1/1,000).

Chlortalidone
In addition to the adverse reactions noted above for Edarclor, the following adverse reactions have been reported for chlortalidone:

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Rare	Thrombocytopenia, leucopenia agranulocytosis, eosinophilia
Metabolism and nutrition disorders	Very common	Rise in blood lipids
	Common	Hypomagnesaemia
	Rare	Hypercalcaemia, glycosuria, worsening of diabetic metabolic state
	Very rare	Hypochloraemic alkalosis
Nervous system disorders	Rare	Headache
Eye disorders	Not known	Choroidal effusion
Cardiac disorders	Common	Postural hypotension
	Rare	Cardiac arrhythmias
Respiratory, thoracic and mediastinal disorders	Rare	Idiosyncratic pulmonary oedema
Gastrointestinal disorders	Common	Loss of appetite, minor gastrointestinal distress
	Rare	Constipation, gastric pain
	Very rare	Pancreatitis
Hepatobiliary disorders	Rare	Intrahepatic cholestasis or jaundice
Skin and subcutaneous tissue disorders	Common	Urticaria
	Rare	Photosensitisation, cutaneous vasculitis
Renal and urinary disorders	Rare	Allergic interstitial nephritis
Reproductive system and breast disorders	Common	Impotence

Description of selected adverse reactions

Renal impairment and renal failure were reported uncommonly in conjunction with blood creatinine increased; the majority was reversible either on treatment or after discontinuation of Edarclor and none required dialysis.

As with other ARBs, serious angioedema may occur rarely (≥1/10,000 to <1/1,000).

Investigations

Serum creatinine
Increased blood creatinine is a known pharmacologic effect of RAAS blockers, such as ARBs and ACE-inhibitors, and is related to the magnitude of blood pressure reduction. Treatment with Edarclor resulted in a greater incidence of blood creatinine increases, compared with azilsartan medoxomil and chlortalidone. Elevations were transient or non-progressive and reversible, and associated with large blood pressure reductions.

Uric acid
Edarclor was associated with increases in serum uric acid consistent with the known pharmacological effects of diuretics. The uric acid elevations are dose dependent increasing with the chlortalidone dose although reports of gout were infrequent across treatment groups, even in long-term studies.

Hemoglobin and hematocrit
Edarclor was associated with small decreases in hematocrit, hemoglobin levels, and red blood cell count, consistent with the known pharmacological effects of inhibitors of the renin-angiotensin-aldosterone system.

Post-marketing experience

A rare incidence of angioedema has been reported in conjunction with use of Edarclor. No other adverse reactions have been identified in post-marketing spontaneous reports.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is limited information available related to overdosage of Edarclor in humans.

Azilsartan medoxomil

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

If symptomatic hypotension should occur, supportive treatment should be instituted and vital signs monitored. Azilsartan is not removed by dialysis.

Chlortalidone

Symptoms of chlortalidone overdose include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA09.

Edarclor is a combination of two antihypertensive agents with complementary mechanisms to control blood pressure: the prodrug of an angiotensin II AT1 receptor antagonist, azilsartan medoxomil, and a thiazide-like diuretic, chlortalidone.

Mechanism of action and pharmacodynamic effect
Azilsartan medoxomil is an orally administered prodrug that is rapidly converted by esterases in the gastrointestinal tract and/or during absorption to the active moiety, azilsartan, which selectively antagonises the effects of angiotensin II by blocking its binding to the AT1 receptor in multiple tissues (see section 5.2). 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 AT1 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.

Chlortalidone produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the early convoluted part of the distal renal tubule in the nephron. The diuretic effect of chlortalidone is due to inhibition of sodium reabsorption inhibiting Na^+Cl^- reabsorption by antagonising the Na^+Cl cotransporter at that site which leads to increased sodium and water excretion

Clinical efficacy and safety

Clinical efficacy

Nearly additive reduction of blood pressure provided by the individual components was observed across the therapeutic dose range that persists for 24 hours.

In an 8-week, multicenter, randomized, double-blind, active-controlled, parallel group factorial study, 1714 patients with moderate to severe essential hypertension were randomized to one of the 11 active treatment arms that compared the relative effect on blood pressure of Edarclor with the respective monotherapy components without titration. Edarclor treatment combinations resulted in significantly greater reduction in systolic and diastolic blood pressure compared with the respective individual monotherapies as determined by clinic blood pressure measurements (see Table 1). Ambulatory blood pressure monitoring (ABPM) of trough blood pressure (22-24 hours post-dose) had similar results.

Table 1. Mean Change from Baseline in Clinic Systolic/Diastolic Blood Pressure (mm Hg) at Week 8

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

In a multicenter, randomized, double-blind, active-controlled, parallel group study of patients with grade 2 or 3 hypertension, not controlled adequately on azilsartan medoxomil 40 mg, target clinic systolic blood pressure (<140 mm Hg for the general population and <130 mm Hg for those with diabetes or CKD) was achieved in 63% of patients treated with azilsartan medoxomil and chlortalidone 40 mg/12.5 mg and 78% of patients treated with azilsartan medoxomil and chlortalidone 40 mg/25 mg, compared to 35% of patients remaining on azilsartan medoxomil 40 mg. Following an initial 4-week treatment with Edarbi 40 mg, treatment with Edarclor of those subjects whose blood pressure remained equal to or higher than 140 mm Hg resulted in a reduction in systolic/diastolic blood pressure of 15.8/7.7 mm Hg (40 mg/12.5 mg) and 21.1/10.3 mm Hg (40 mg/25 mg) compared to patients who remained on azilsartan medoxomil 40 mg of 6.4/3.2 mm Hg.

In two randomized, double-blind titration studies, azilsartan medoxomil and chlortalidone produced greater reduction in systolic and diastolic blood pressure compared to olmesartan medoxomil/hydrochlorothiazide in patients with moderate to severe hypertension.

Edarclor's blood pressure lowering effects are maintained throughout the 24-hour period, with most of the antihypertensive effect of Edarclor occurring within 1-2 weeks of dosing and being maintained for up to 12 months of evaluation.

Edarclor led to robust reductions in all blood pressure parameters across diverse subgroups including age, gender, or race. In black patients in particular, treatment with Edarclor resulted in blood pressure reductions that were generally similar to the overall population, despite a known attenuated response to RAAS blockade in this population.

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 azilsartan medoxomil.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Edarclor (azilsartan medoxomil/chlortalidone) in all subsets of the paediatric population in hypertension as per Paediatric Investigation Plan (PIP) decision (EMA/PDCO/430493/2012), in the granted indication (see section 4.2 for information on paediatric use).

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 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.

5.2 Pharmacokinetic properties

Concomitant administration of azilsartan 80 mg and chlortalidone 25 mg once daily for 7 days does not affect the PK of either substance in healthy subjects.

Following oral administration of the fixed dose tablet, the peak plasma concentration (C_{max}) of chlortalidone is 45% higher compared to administration of chlortalidone and azilsartan as separate tablets. The extent of absorption as defined by the area under the curve (AUC) of both azilsartan and chlortalidone following administration of Edarclor is similar to that when azilsartan and chlortalidone are administered as separate tablets.

Edarclor may be administered with or without food.

The following section outlines the pharmacokinetic properties of the individual components of Edarclor (azilsartan medoxomil/chlortalidone) as reported in their respective Summary of Product Characteristics.

Absorption

Azilsartan medoxomil

Following oral administration, azilsartan medoxomil is rapidly hydrolyzed to azilsartan, the active metabolite, in the gastrointestinal tract during absorption. Azilsartan medoxomil is not detected in plasma after oral administration. 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.

The estimated absolute oral bioavailability of azilsartan medoxomil based on plasma levels of azilsartan is approximately 60%. After oral administration of azilsartan medoxomil, the time to maximal concentration (T_{max}) of azilsartan is reached within 1.5 to 3 hours. Food does not affect the bioavailability of azilsartan (see section 4.2).

Chlortalidone

The estimated bioavailability of chlortalidone is approximately 64%, after 8 to 12 hours post dose. On repeated daily doses of 50 mg, mean steady state blood concentration of 7.2 µg/ml (21.2 µmo/L), measured at the end of the 24 hour dosage interval, is reached after 1 to 2 weeks.

Distribution

Azilsartan medoxomil

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.

Chlortalidone

In whole blood, chlortalidone is predominantly bound to erythrocyte carbonic anhydrase. In vitro, plasma protein binding of chlortalidone is approximately 76%, with the major binding protein being albumin.

Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50 mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood were about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Biotransformation

Azilsartan medoxomil

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 Edarclor. The major enzyme responsible for azilsartan metabolism is CYP2C9.

Chlortalidone

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.

Elimination

Azilsartan medoxomil

Following an oral dose of 14C-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.

Chlortalidone
Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60 ml/min.

Linearity/non-linearity
Azilsartan medoxomil
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.

Chlortalidone
For doses of 25 mg and 50 mg, C_{max} values average 1.5 µg/ml (4.4 µmol/L) and 3.2 µg/ml (9.4 µmol/L) respectively. For doses up to 100 mg there is a proportional increase in AUC.

Special populations

Paediatric population
The pharmacokinetics of azilsartan has been studied in paediatric subjects with hypertension, between the ages of 4 to 16 years. However, safety and efficacy in paediatric patients has not been established.

The pharmacokinetics of chlortalidone is not available in children under 18 years of age.

Older population
Pharmacokinetics of azilsartan does not differ significantly between young (age range 18-45 years) and elderly (age range 65-85 years) patients.
In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, caution is recommended when treating the very elderly (≥75 years) with Edarclor (see section 4.2).

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 (GFR <30 mL/min/1.73m^2) or end stage renal disease (see section 4.2). Haemodialysis does not remove azilsartan from the systemic circulation.

The major part of an absorbed dose of chlortalidone is excreted by the kidneys; however renal dysfunction does not alter the pharmacokinetics of chlortalidone. The rate-limiting factor in the elimination of chlortalidone from blood or plasma is most probably the affinity of the drug to the carbonic anhydrase of erythrocytes. As a result, no dosage adjustment is needed for Edarclor in patients with mild and moderately impaired renal function (GFR ≥30-< 90 mL/min/1.73 m^2).

Hepatic impairment
Administration of azilsartan medoxomil for up to 5 days in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment resulted in a 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. Chlortalidone has not been studied in patients with hepatic impairment.

Edarclor is contraindicated in patients with severely impaired hepatic function (see section 4.2).

Gender
Pharmacokinetics of azilsartan does not differ significantly between males and females. In a population pharmacokinetic analysis of patients with hypertension receiving Edarclor, male subjects had a lower exposure (C_{max} and AUC) than female subjects (≤30%). The differences in pharmacokinetics are not considered clinically relevant.
No dose adjustment is necessary based on gender.

Race
Pharmacokinetics of azilsartan does not differ significantly between black and white populations. In a population pharmacokinetic analysis of patients with hypertension receiving Edarclor, there was no effect of race on the pharmacokinetics of azilsartan or chlortalidone.
No dose adjustment is necessary based on race.

5.3 Preclinical safety data

Azilsartan medoxomil/chlortalidone

No mutagenicity, carcinogenicity or fertility studies have been conducted with the combination of azilsartan medoxomil and chlortalidone.

The decreased plasma potassium levels and renal corticomedullary mineralization attributed to chlortalidone treatment were not observed after treatment with chlortalidone, azilsartan medoxomil and M-II in combination. There were no unexpected or unique toxicities associated with dosing of the combination.

In an embryo-fetal developmental study in rats, there was no teratogenicity or increase in fetal mortality in the litters of dams receiving azilsartan medoxomil, M-II and chlortalidone concomitantly during the period of organogenesis at maternally toxic doses.

Azilsartan medoxomil

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 blockers, 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 reproductive and developmental toxicity studies, there were no effects on male or female fertility and no evidence of a teratogenic effect in rats or rabbits. However, in peri- and post-natal animal studies, in which dosing of pregnant animals was continued through lactation, some hazardous potential to the postnatal development of the offspring was seen, such as lower body weight, a slight delay in physical development (delayed incisor eruption, pinna detachment, eye opening), and higher rates of mortality. Azilsartan and M-II showed no evidence of mutagenicity or relevant clastogenic activity in *in vitro or in vivo* studies and no evidence of carcinogenicity in rats or mice.

Chlortalidone

Reports in the literature indicate that treatment with chlortalidone does not produce reproductive toxicity in dams or cause embryo-fetal mortality or teratogenicity in pregnant mice, rats, hamsters or rabbits. Chlortalidone has been demonstrated to be a safe and effective prophylactic treatment for toxemia in gravid women at least 30 weeks pregnant and at high risk for developing the condition.

Environmental Risk Assessment
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Fumaric acid (E 297) (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Hydroxypropylcellulose (E 463)
Crospovidone (Type A)
Cellulose, microcrystalline (E 460)
Magnesium stearate (E 572)
Titanium dioxide (E171)
Iron oxide, red (E172)
Hypromellose 2910
Talc
Macrogol 8000

Printing ink grey F1:
Shellac
Iron oxide, black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Cartons containing desiccated or non-desiccated aluminum/aluminum blister packs (contains PE and PVC).

Pack sizes:

One blister pack contains 14 tablets.

14, 28 or 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Edarclor 40 mg/12,5 mg, filmomhulde tabletten	RVG 116373
Edarclor 40 mg/25 mg, filmomhulde tabletten,	RVG 116387

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 25 november 2015
Datum van laatste verlenging: 30 januari 2019

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft de rubrieken 4.4 en 7; 9 december 2021

Detailed information on this medicinal product is available on the website of College ter Beoordeling van Geneesmiddelen, http://www.cbg-meb.nl/