

1.3.1	Enalapril maleate
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 2.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg enalapril maleate.

Excipient with known effect: lactose monohydrate 64.90 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Round, white, tablet with bevelled edges and a diameter of 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of hypertension
- Treatment of symptomatic heart failure
- Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction (ejection fraction $\leq 35\%$)

(See section 5.1).

4.2 Posology and method of administration

Posology

The absorption of <Invented name> tablets is not affected by food.

The dose should be individualized according to patient profile (see section 4.4) and blood pressure response.

Hypertension

The initial dose is 5 mg to maximally 20 mg, depending on the degree of hypertension and the patient's condition (see below). <Invented name> should be given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with strongly activated renin-angiotensin-aldosterone system (e.g. renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience excessive blood pressure fall following the

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initial dose. A starting dose of 5 mg or lower is recommended in these patients and initiation of the treatment should take place under medical supervision.

Prior treatment with high doses of diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in these patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with <Invented name>. Renal function and serum potassium should be monitored.

The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

Heart failure/asymptomatic left ventricular dysfunction

In the management of symptomatic heart failure, <Invented name> is used together with diuretics and, where appropriate, digitalis or beta blockers. The initial dose of <Invented name> in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of or after effective management of symptomatic hypotension following initiation of therapy with <Invented name> in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg. The maintenance dose should be given as a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a period of 2 to 4 weeks. The maximum dose is 40 mg daily given in two divided doses.

Suggested dosage titration of <Invented name> in patients with heart failure/asymptomatic left ventricular dysfunction

Week	Dose mg/day
Week 1	Day 1 to 3: 2.5 mg/day* as a single dose Day 4 to 7: 5 mg/day as two divided doses
Week 2	10 mg/day as a single dose or as two divided doses
Week 3 and 4	20 mg/day as a single dose or as two divided doses

*Special caution should be followed in patients with impaired renal function or concomitantly taking diuretics (see 4.4 Special warnings and precautions for use).

Blood pressure and renal function should be monitored closely both before and after starting treatment with <Invented name> (see 4.4 Special warnings and precautions for use) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before starting treatment with <Invented name>. Appearance of hypotension after the initial dose of <Invented name> does not imply that hypotension will recur during chronic therapy with <Invented name> and does not preclude continued use of the drug. Serum potassium and renal function should also be monitored.

Patients with renal impairment

Generally, the intervals between administration of enalapril should be prolonged and/or the dosage reduced.

Creatinine clearance (CrCL) ml/min	Initial dose in mg/day
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30<CrCL<80 ml/min	5 - 10 mg
10<CrCL≤30 ml/min.	2.5 mg
CrCL≤10 ml/min.	2.5 mg on dialysis days*

* See 4.4 Special warnings and precautions for use – Haemodialysis Patients.

Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted in accordance with the blood pressure response.

Elderly patients

The dose should be adjusted according to the renal function in the elderly patients (see section 4.4).

Paediatric population

There is limited clinical trial experience from the use of <Invented name> in hypertensive paediatric patients (see sections 4.4, 5.1 and 5.2).

For patients who can swallow tablets, the dose should be individualised according to the patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients weighing 20 to <50 kg and 5 mg in patients weighing ≥50 kg. <Invented name> should be given once daily. The dosage should be adjusted according to the patient's need to a maximum of 20 mg daily in patients weighing 20 to <50 kg and 40 mg in patients weighing ≥50 kg. (See 4.4 Special warnings and precautions for use).

<Invented name> is not recommended for use in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimester of pregnancy (see section 4.4 and 4.6).
- The concomitant use of <Invented name> with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. <Invented name> must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving <Invented name>, symptomatic hypotension is more likely to occur if the patient has been volume depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see sections 4.5 and 4.8). In patients with heart failure, with or without concomitant renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of <Invented name> and/or diuretic is adjusted. Similar considerations may apply to patients with ischaemic heart

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or cerebrovascular disease when an excessive fall in blood pressure may result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, intravenous infusion of normal saline should be administered. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with <Invented name>. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or <Invented name> may become necessary.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy

As with all vasodilators, ACE inhibitors should be given with caution to patients with left ventricular outflow obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

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.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril and has mainly affected patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with enalapril therapy is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine levels when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may become necessary. This situation may possibly increase the incidence of an underlying artery stenosis (see section 4.4, Renovascular hypertension).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

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Kidney transplantation

There is no experience from the administration of <Invented name> to patients who have recently undergone a kidney transplantation. Treatment with <Invented name> is therefore not recommended.

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not known. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the treatment with ACE inhibitors and receive appropriate medical follow-up.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressive therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially in connection with pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in these patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including <Invented name>. This may occur at any time during the treatment. In such cases, <Invented name> should be immediately discontinued and appropriate monitoring should be instituted to ensure complete resolution of symptoms before the patient is discharged. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may be insufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. When the tongue, glottis or larynx are involved, there is a risk of airway obstruction. Appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while using ACE inhibitors. (Also see section 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of enalapril. Treatment with enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used

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when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during hymenoptera desensitisation

Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Hemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69®) and concomitantly treated with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Hypoglycemia

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See section 4.5).

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be caused by this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim /sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium.

Hyperkalemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Lithium

The combination of lithium and enalapril is generally not recommended (see section 4.5).

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Paediatric population

There is limited efficacy and safety experience in hypertensive children > 6 years of age, and no experience from the other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see section 4.2, 5.1 and 5.2). <Invented name> is not recommended in children for other indications than hypertension.

<Invented name> is not recommended for use in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available. (See section 4.2).

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitors 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see section sections 4.3 and 4.6).

Ethnic differences

Like other angiotensin-converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Lactose

<Invented name> contains lactose. Patients with rare hereditary problems of lactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Sacubitril/valsartan

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with enalapril. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium levels. Care should also be taken when enalapril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of enalapril with the above-mentioned drugs is not recommended. If concomitant use is indicated because of documented hypokalaemia, these should be used with caution and with frequent monitoring of serum potassium levels (see section 4.4).

Diuretics (thiazide or loop diuretics)

Prior treatment with high doses of diuretics may result in volume depletion and lead to a risk of hypotension when initiating therapy with enalapril (see section 4.4). The hypotensive effects can be reduced by discontinuing the diuretic therapy, by volume expansion or salt intake or by initiating therapy with low doses of enalapril.

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Other antihypertensive agents

Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

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).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves to be necessary, serum lithium levels should be carefully monitored (see section 4.4).

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant treatment with ACE inhibitor therapy including enalapril.

Racecadotril, Mammalian Target of Rapamycin (mTOR) Inhibitors and vildagliptin

Patients taking concomitant ACE inhibitors with racecadotril, mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies suggest that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect

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with a risk of hypoglycaemia. This phenomenon appeared to occur more likely during the first weeks of combined treatment and in patients with renal impairment. (See sections 4.4 and 4.8)

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Acetylsalicylic acid, thrombolytics and beta blockers

Enalapril can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and beta blocker.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.

Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

ACE inhibitors therapy exposure during the second and third trimesters is known to induce human foetotoxicity (renal failure, oligohydramnios, skull ossification retardation) and neonatal toxicity (decreased renal function, hypotension, hyperkalaemia). (See section 5.3). Maternal oligohydramnios, presumably representing decreased fetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see section 4.3 and 4.4).

Breast-feeding

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2).

Although these concentrations seem to be clinically irrelevant the use of <Invented name> in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical

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experience. In case of an older infant the use of Enalapril in breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occur occasionally.

4.8 Undesirable effects

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			anaemia (including aplastic and haemolytic)	neutropenia, decreases in haemoglobin levels, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases		
Endocrine disorders						syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders			hypoglycaemia (see 4.4 Special warnings and precautions for use, Diabetic patients)			
Psychiatric disorders		depression	confusion, insomnia, nervousness	dream abnormalities, sleep disorders		

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Nervous system disorders	dizziness	headache, syncope, taste alteration	somnolence, paraesthesia, vertigo			
Eye disorders	blurred vision					
Ear and labyrinth disorders			tinnitus			
Cardiac disorders		chest pain, rhythm disturbances, angina pectoris, tachycardia	palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)			
Vascular disorders		hypotension (including orthostatic hypotension)	flushing, orthostatic hypotension	Raynaud's phenomenon		
Respiratory, thoracic and mediastinal disorders	cough	dyspnoea	rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma	pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia		
Gastrointestinal disorders	nausea	diarrhoea, abdominal pain	ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritation, dry mouth, peptic ulcer	stomatitis/aphtous ulcerations, glossitis	intestinal angioedema	
Hepatobiliary disorders				hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)		
Skin and subcutaneous tissue disorders		rash, hypersensitivity/Angioedema: Angioedema of the face,	diaphoresis, pruritus, urticaria, alopecia	erythema multiforme, Stevens-Johnson syndrome,		a symptom complex has been reported

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		extremities, lips, tongue, glottis and/or larynx has been reported (see 4.4 Special warnings and precautions for use)		exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma		which may include some or all of the following: fever, serositis, vasculitis, myalgia/ myositis, arthralgia/ arthritis, a positive ANA titer, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity and other dermatological manifestations may occur
Musculoskeletal, connective tissue, and bone disorders			muscle cramps			
Renal and urinary disorders			renal dysfunction, renal failure, proteinuria	oliguria		
Reproductive system and breast disorders			impotence	gynecomastia		
General disorders and administration site conditions	asthenia	fatigue	malaise, fever			
Investigations		hyperkalaemia, increases in serum creatinine levels	increases in blood urea, hyponatraemia	elevations of liver enzymes, elevations of serum bilirubin		

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* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

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

Symptoms

Limited data are available on overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, appearing about six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100 and 200 times higher than normally seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril.

Management

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, measures aiming at an elimination of enalapril maleate (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate) should be taken. Enalaprilat may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant tachycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored regularly.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, ATC code: C09AA02.

Mechanism of action

<Invented name> (enalapril maleate) is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. *Angiotensin converting enzyme* (ACE) is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat that inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreases aldosterone secretion.

ACE is identical to kininase II. Thus, <Invented name> may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role of this in the therapeutic effects of <Invented name> remains to be elucidated.

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Although the mechanism through which <Invented name> lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, <Invented name> is antihypertensive even in patients with low-renin hypertension.

Pharmacodynamic effects

Administration of <Invented name> in patients with hypertension results in reduction of blood pressure in both supine and standing position without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients, reaching the optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of <Invented name> has not been associated with rebound blood pressure.

Effective ACE inhibition usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen after one hour, with a peak reduction of blood pressure achieved 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to last for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in the heart rate. Following administration of <Invented name>, there was an increase in renal blood flow; glomerular filtration rate (GFR) was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

In short-term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

When <Invented name> is given together with thiazide-type diuretics, the blood pressure-lowering effects of <Invented name> are at least additive. <Invented name> may reduce or prevent the development of thiazide-induced hypokalaemia.

In patients with cardiac insufficiency treated with digitalis and diuretics, dosage of oral or intravenous <Invented name> is associated with a reduction in peripheral resistance and blood pressure. Cardiac output increased, while heart frequency dropped (usually increased in patients with cardiac insufficiency). Pulmonary capillary pressure was also reduced. There was a beneficial effect to the severity of heart failure as measured according to NYHA (New York Heart Association) criteria and exercise tolerance tests and these effects were maintained during continuous treatment.

In patients with mild to moderate cardiac insufficiency, enalapril delayed the progressive heart dilatation/enlargement and cardiac insufficiency. This was measured as reduced left ventricular diastolic and systolic volume and an improvement in ejection fraction.

Clinical efficacy and safety

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Prevention Trial) investigated a population with asymptomatic left ventricular dysfunction (LVEF<35 %). 4228 patients were randomised to receive either placebo (n=2117) or enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the enalapril group (29.8%) (risk reduction: 29%, 95% CI: 21 - 36%; p<0.001). 518 patients in the placebo group (24.5%) and 434 in

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the enalapril group (20.6%) died or were hospitalised for a new or worsening heart failure (risk reduction 20%; 95% CI: 9–30%; $p < 0.001$).

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Prevention Trial) investigated a population with chronic symptomatic cardiac failure due to systolic dysfunction ($LVEF < 35\%$). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo ($n=1284$) or enalapril ($n=1285$). In the placebo group, there were 510 deaths (39.7%) as compared with 452 in the enalapril group (35.2%) (risk reduction: 16%, 95% CI: 5 - 26%; $p < 0.0036$). There were 461 cardiovascular deaths in the placebo group as compared with 399 in enalapril group (risk reduction: 18%; 95% CI: 6–28%; $p < 0.002$), mainly due to a reduction in deaths for progressive heart failure (251 in the placebo group vs 209 in the enalapril group, risk reduction 22%, 95% CI: 6–35%). Fewer patients died or were hospitalised for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction 26%; 95% CI: 18–34%; $p < 0.0001$). Overall in SOLVD study in patients with left ventricular dysfunction, <Invented name> reduced the risk of myocardial infarction by 23% (95% CI: 11–34%; $p < 0.001$) and reduced the risk of hospitalisation for unstable angina pectoris by 20% (95% CI: 9–29%; $p < 0.001$).

Dual Blockade of the renin-angiotensin-aldosterone system (RAAS)

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

There is limited experience from the use in hypertensive paediatric patients > 6 years of age. In a clinical study involving 110 hypertensive paediatric patients 6 to 16 years of age with a body weight ≥ 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m², patients who weighed < 50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥ 50 kg received either 1.25, 5 or 40 mg of enalapril daily. Administration of enalapril once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse effect profile for paediatric patients was not different from that seen in adult patients.

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5.2 Pharmacokinetic properties

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablets is approximately 60%. The absorption is not influenced by the presence of food in the gastro-intestinal tract.

Following absorption, enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent ACE inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

Distribution

Over the concentration range that is therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60%.

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination

Excretion of enalaprilat is primarily renal. The principle components in urine are enalaprilat (about 40% of the dose) and intact enalapril (about 20%).

Renal impairment

Exposure to enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min), the steady-state AUC of enalaprilat was approximately two-fold compared to that in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), AUC was increased approximately to 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady-state is delayed. (See 4.2 Posology and method of administration). Enalaprilat may be removed from the general circulation by haemodialysis. The dialysis clearance is 62 ml/min.

Children and adolescents

A multiple-dose pharmacokinetic study was conducted in 40 hypertensive male and female paediatric patients aged 2 months to ≤ 16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. There were no major differences in the pharmacokinetics of enalaprilat in children compared with historic data on adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady-state, the mean effective half-life for accumulation of enalaprilat was 14 hours.

Lactation

After an oral single dose of 20 mg for five women in postpartum period the average of the highest concentration of enalapril in milk 1.7 µg/L (in the interval between 0.54 to 5.9 µg/L) 4-6 hours after the dose. The average of the highest concentrations of enalaprilat was 1.7 µg/L (in the interval between 1.2 to 2.3 µg/L); the highest concentrations was found in different moments during a 24 hours period. Data from the highest concentrations in milk gave an estimated value for the highest intake for

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a child who exclusively nurse approximately 0.16% of the weight adjusted dose of the mother. A woman that had taken a daily dose of 10 mg enalapril during 11 months had the highest concentrations of enalapril of 2 µg/L in the milk, 4 hours after one dose and the highest concentrations of enalaprilat 0.75 µg/L approximately 9 hours after the dose. The total amount of enalapril and enalaprilat estimated in milk during a 24-hours period was 1.44 µg/L respectively 0.63 µg/L. After a single dose of 5 mg to a mother and 10 mg to 2 mothers there were no demonstrable concentrations of enalaprilat (<0.2 µg/L) after 4 hours; the concentrations were not decided.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicology studies suggest that enalapril has no effect on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats received a dose prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and to be excreted into the breast milk. ACE inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Maize starch
Talc
Hydroxypropylcellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister (Polyamide/Alu/PVC/Alu): 28, 30, 50, 60, 98, 100 and 100x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2019-06-27