SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AQUMELDI 0.25 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 0.25 mg of enalapril maleate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

White, round, biconvex orodispersible tablets, 2 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AQUMELDI is indicated for the treatment of heart failure in children from birth to less than 18 years.

4.2 Posology and method of administration

AQUMELDI should be initiated by a physician experienced in the treatment of paediatric patients with heart failure.

Posology

Starting/test dose

0.01 to 0.04 mg/kg (max 2 mg) as a single initial dose.

- Before giving a test dose, blood pressure (BP) and renal function should be checked. If the BP is below the 5th percentile or creatinine is above normal limit for age, then enalapril should not be given.
- Test dose should be at the lower end of the range for less stable patients and in infants <30 days of age.
- Blood pressure should be monitored at intervals for 1–2 hours after the initial dose. If systolic BP is below the 5th percentile enalapril should be stopped and appropriate clinical care given.

Target/maintenance dose

0.15 to 0.3 mg/kg (max 20 mg) per day in one or two divided doses 8 hours after test dose.

The dose should be individualised according to blood pressure, serum creatinine and potassium response.

- If systolic blood pressure (SBP) is greater than or equal to the 5th percentile and serum creatinine is no more than 1.5 × baseline, consider enalapril dose up-titration.
- If SBP is below the 5th percentile and serum creatinine is more than 2 × baseline, enalapril should be stopped.
- If systolic blood pressure is below the 5th percentile and serum creatinine is between 1.5 and 2 × baseline, enalapril dose should be titrated down.
- If SBP is above the 5th percentile and serum creatinine is more than 2 × baseline, enalapril dose should be titrated down.
- If systolic blood pressure is greater than or equal to the 5th percentile and serum creatinine is between 1.5 to 2 × baseline the enalapril should be continued at the same dose.

At any stage if potassium ≥ 5.5 mmol/l pause enalapril treatment. Once hyperkalaemia has resolved, restart enalapril on the same or a lower dose level. If hyperkalaemia recurs, repeat the above and restart at a lower level. If potassium is repeatedly above 5.5 mmol/l, despite multiple dose decreases, discontinue enalapril.

If a dose of AQUMELDI is missed the next dose should be given as usual. Do not give a double dose to make up for a forgotten dose.

Special populations

Renal impairment

Special precautions should be followed in patients with impaired renal function (see section 4.3 and 4.4):

- Enalapril is contraindicated in paediatric patients with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 (see section 4.3).
- GFR ≥50 ml/min/1.73 m^2: Dose adjustment not required.
- GFR ≥30-<50 ml/min/1.73 m^2: Start with 50% of the single dose and dose at 12 hour intervals.
- For dialysis: Start with 25% of the normal single dose and dose at 12 hour intervals.

The dose should be increased to the highest possible tolerated dose depending on the effect. Depending on the clinical condition of the patient, the creatinine and potassium concentrations should be checked within 2 weeks after the start of treatment and then at least once a year.

Hepatic impairment

No data is available for treatment of paediatric subjects with liver impairment. Dose adjustment is not considered necessary however such children should only be treated with enalapril under strict monitoring. Treatment of children below the age of 1 month with hepatic impairment is not recommended (see section 4.4).

Children less than 30 days of age

Treatment of infants < 30 days of age should only be conducted with rigorous monitoring, including blood pressure, serum potassium levels and renal function.

Method of administration

For oral use only. Place on the tongue or in the buccal cavity and allow to disperse.

AQUMELDI can be taken with or without meals.

For instructions on administering starting doses < 0.25 mg and in case of feeding tube administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or any other angiotensin converting enzyme inhibitor (ACEi).
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of AQUMELDI with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Combination with sacubitril/valsartan (a medicinal product containing a neprilysin inhibitor) due to the increased risk of angioedema. AQUMELDI is not to be administered within 36 hours of switching to or from sacubitril/valsartan (see sections 4.4 and 4.5).
- Paediatric patients with severe renal impairment (GFR <30 ml/min/1.73 m^2) (see section 4.2).

4.4 Special warnings and precautions for use

Symptomatic hypotension

In patients with heart failure, with or without associated 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 AQUMELDI and/or diuretic is adjusted. Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with AQUMELDI. 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 AQUMELDI may be necessary.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy

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

Renal impairment

Renal failure has been reported in association with enalapril and has been seen mainly in 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 (see section 4.8).

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dose reduction of enalapril and/or discontinuation of the diuretic may be required (see section 4.2). This situation should raise the possibility of underlying renal artery stenosis (see renovascular hypertension below).

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.

Kidney transplantation

There is no experience regarding the administration of AQUMELDI in patients with a recent kidney transplantation. Treatment with AQUMELDI is therefore not recommended.

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor 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, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is 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 such 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 enalapril. This may occur at any time during treatment. In such cases, AQUMELDI must be discontinued promptly, and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. 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 not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1 000 (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 receiving an ACE inhibitor (see section 4.3).

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

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.5). The combination of enalapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril therapy. If treatment with

sacubitril/valsartan is stopped, enalapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

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 sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Haemodialysis patients

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

Hypoglycaemia

Diabetic patients treated with oral antidiabetics or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see section 4.5).

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the 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 medicinal products that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalaemia include those patients 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 medicinal products associated with increases in serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole). Neonates are at increased risk of developing hyperkalaemia. The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicinal products that may increase serum potassium, particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Lithium

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

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). 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 be 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.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors must be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Ethnic differences

As with other ACE inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-black, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Paediatric population

AQUMELDI is not recommended in children in indications other than heart failure.

Caution is advised in children below 1 month of age as they may be very sensitive to the medical product. Data on the use of Aqumeldi in children below 1 month of age in the clinical studies is scarce (n=4). Any signs of adverse events and electrolytes should be closely monitored.

Hepatic impairment

No data is available for treatment of paediatric subjects with pre-existing liver conditions. Therefore, paediatric subjects with pre-existing liver conditions should only be treated with enalapril under strict monitoring. Treatment of children below the age of 1 month with hepatic impairment is not recommended.

Sodium

This medicinal product 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

No interaction studies have been performed with AQUMELDI in the adult or paediatric population. Interaction studies with enalapril have only been performed in adults.

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

Clinical study data have 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).

Potassium sparing diuretics, potassium supplements, or other medicinal products that may increase serum potassium

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes, or other medicinal products that may increase serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole) may lead to significant increases in serum potassium. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Diuretics (thiazide or loop diuretics)

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

Antihypertensives

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

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 enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (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 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 antihypertensives. 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 ACE inhibitor therapy including enalapril.

Mammalian target of rapamycin (mTOR) inhibitors

Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see section 4.4).

Neprilysin inhibitors

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.4). The concomitant use of enalapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of enalapril therapy. Enalapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetics (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This

phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see sections 4.4 and 4.8). Patients taking concomitant vildagliptin therapy may be at increased risk for angioedema (see section 4.4).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, thrombolytics and β-blockers

Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

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

Based on human experience ACE inhibitors including enalapril cause congenital malformations (decreased renal function, oligohydramnios, skull ossification retardation, limb contractures, craniofacial deformations and hypoplastic lung development) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) when administered during pregnancy.

AQUMELDI is contraindicated during the second and third trimester of pregnancy and is not recommended in the first trimester (see section 4.3 and 4.4).

Women of childbearing potential must use effective contraception during and up to 1 week after treatment.

Maternal oligohydramnios, presumably representing decreased foetal 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 sections 4.3 and 4.4).

Breast-feeding

AQUMELDI and its metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants cannot be excluded (see section 5.2).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from AQUMELDI therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of enalapril on fertility are available. In rats, there was no effect on mating or fertility with enalapril treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

AQUMELDI has minor influence on the ability to drive and use machines. Dizziness or weariness may occur which may affect concentration and co-ordination. This may alter the performance at skilled tasks such as driving, riding a bicycle, or using machines.

4.8 Undesirable effects

Summary of safety profile

The most frequent drug related adverse reactions reported in children were cough (5.7%), vomiting (3.1%), microalbuminuria (3.1%), hyperkalaemia (2.9%), hypotension (1.4%), and postural dizziness (1.2%).

Tabulated list of adverse drug reactions

Children

The adverse reaction frequency listed in Table 1 is derived from the clinical studies in children receiving AQUMELDI for heart failure. In total 86 children in these studies received enalapril for up to 1 year; as such the data are limited.

The adverse reactions are listed below by SOC (system organ class) and by frequency, most frequent reactions first, with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1. List of adverse reactions in children with heart failure.

Adverse reactions	**Frequency**
Nervous system disorders	
Dizziness postural	Common
Vascular disorders	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Gastrointestinal disorders	
Vomiting	Common
Investigations	
Hyperkalaemia	Common
Microalbuminuria	Common

Adults

Enalapril tablets have been evaluated for safety in more than 10 000 adult patients and in controlled clinical studies involving 2 314 hypertensive patients and 363 patients with congestive heart failure. Adverse reactions and frequency in the adult population is listed in Table 2.

Table 2. List of adverse reactions in the adult population

Adverse reactions	**Frequency**
Blood and lymphatic system disorders	
Aplastic anaemia	Uncommon
Haemolytic anaemia	Uncommon
Anaemia	Uncommon
Bone marrow depression	Rare
Neutropenia	Rare
Agranulocytosis	Rare
Pancytopenia	Rare
Thrombocytopenia	Rare

Adverse reactions	**Frequency**
Lymphadenopathy	Rare
Haemoglobin decreased	Rare
Haematocrit decreased	Rare
Immune system disorders	
Angioedema	Common
Autoimmune diseases	Rare
Endocrine disorders	
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Unknown
Metabolism and nutrition disorders	
Hypoglycaemia	Uncommon
Psychiatric disorders	
Depression	Common
Confusion	Uncommon
Nervousness	Uncommon
Insomnia	Uncommon
Abnormal dreams	Rare
Sleep disorders	Rare
Nervous system disorders	
Dizziness	Very common
Headache	Common
Syncope	Common
Taste alteration	Common
Paraesthesia	Uncommon
Somnolence	Uncommon
Vertigo	Uncommon
Eye disorders	
Blurred vision	Very common
Ear and labyrinth disorders	
Tinnitus	Uncommon
Cardiac disorders	
Chest pain	Common
Rhythm disturbances	Common
Angina pectoris	Common
Tachycardia	Common
Myocardial infarction	Uncommon
Cerebrovascular accident	Uncommon
Palpitations	Uncommon
Vascular disorders	
Hypotension	Common
Orthostatic hypotension	Uncommon
Flushing	Uncommon
Raynaud’s phenomenon	Rare
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnoea	Common
Asthma	Uncommon
Bronchospasm	Uncommon
Sore throat	Uncommon
Rhinorrhoea	Uncommon
Hoarseness	Uncommon
Pulmonary infiltrates	Rare

Adverse reactions	**Frequency**
Allergic alveolitis	Rare
Eosinophilic pneumonia	Rare
Rhinitis	Rare
Gastrointestinal disorders	
Nausea	Very common
Diarrhoea	Common
Abdominal pain	Common
Vomiting	Common
Ileus	Uncommon
Pancreatitis	Uncommon
Peptic ulcer	Uncommon
Constipation	Uncommon
Anorexia	Uncommon
Gastric irritation	Uncommon
Dyspepsia	Uncommon
Dry mouth	Uncommon
Stomatitis	Rare
Aphthous ulceration	Rare
Glossitis	Rare
Intestinal angioedema	Very rare
Hepatobiliary disorders	
Hepatic failure	Rare
Cholestasis	Rare
Hepatitis	Rare
Skin and subcutaneous tissue disorders	
Rash	Common
Pruritis	Uncommon
Diaphoresis	Uncommon
Alopecia	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Rare
Exfoliative dermatitis	Rare
Toxic epidermal necrolysis	Rare
Pemphigus	Rare
Erythroderma	Rare
Severe skin reactions*	Unknown
Hypersensitivity reactions	Unknown
Musculoskeletal and connective tissue disorders	
Muscle cramps	Uncommon
Renal and urinary disorders	
Renal failure	Uncommon
Renal dysfunction	Uncommon
Proteinuria	Uncommon
Oliguria	Rare
Reproductive system and breast disorder	
Impotence	Uncommon
Gynaecomastia	Rare
General disorders and administration site conditions	
Aesthenia	Very common
Fatigue	Common
Fever	Uncommon
Malaise	Uncommon

Adverse reactions	Frequency
Investigations	
Hyperkalaemia	Common
Microalbuminuria	Common
Increased serum creatinine	Common
Increased blood urea	Uncommon
Hyponatraemia	Uncommon
Increased liver enzymes	Rare
Increased serum bilirubin	Rare

* A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Paediatric population

Blood pressure and heart rate

Following the first ingestion of AQUMELDI no changes were reported in blood pressure or heart rate in naïve or ACEi pre-treated paediatric heart failure patients during the 8-h observation period. Over the first 8 weeks of treatment, mean values of blood pressure did not change over time. The same trend was observed for heart rate. Mean arterial pressure (MAP), based on systolic and diastolic blood pressure, increased in every age group throughout the duration of the subsequent 10-month study period except for children aged 6-12 months where it showed a minor decrease.

Renal safety parameters

Over the 12-month study period treatment, serum creatinine, blood urea nitrogen (BUN), GFR and potassium levels were generally within normal range and constant in paediatric patients with heart failure. The only difference being in children aged from birth to 3 months where BUN levels were significantly higher at the end of the study compared to the start, mean (± standard deviation (SD)) 4.4 (±1.8) vs 2.8 (±1.4), p=0,0001). In paediatric patients with heart failure, microalbuminuria was consistently reported in only one patient with dilated cardiomyopathy from the first study visit. As this patient prematurely left the study and was lost to follow-up, only limited data are available. Microalbuminuria was incidentally reported in three other cases, but at other visits microalbumin was within normal range. For the remaining patients values were similar in all age groups throughout the study.

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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Limited data are available for overdose of enalapril in adults and there is no specific data in children. The most prominent features of overdose reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively.

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution for injection. 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, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulfate). Enalapril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, plain, ATC code: C09AA02.

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline.

Mechanism of action

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

After oral administration in adults, enalapril is hydrolysed via hepatic CES 1 to the active metabolite enalaprilat, which acts as an ACE inhibitor. ACE is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the vasoconstrictor substance angiotensin II and hence inhibition of ACE results in decreased plasma angiotensin II. This also leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion. The mechanism of action of enalapril is therefore primarily via the suppression of the RAAS. However, ACE is identical to kininase II, and so enalapril may also exert its effects by blocking the degradation of bradykinin, a potent vasodepressor peptide. Questions remain regarding the differential effects of ACE inhibition on RAA axis depending on the paediatric age range in question.

Pharmacodynamic effects

Exploratory pharmacodynamics for brain natriuretic peptides (Nt-proBNP), shortening fraction and RAAS associated with enalapril orodispersible tablets in children with heart failure were studied in two clinical studies; 32 children aged 1 month to <12 years with heart failure due to dilated cardio myopathy (DCM) (WP08) and 70 children aged birth to 6 years with heart failure due to congenital heart disease (CHD) (WP09). Mean age 555 days, mean weight 8.92 kg and height 74.01 cm. 46% were females and 54% were males. The data are presented below.

In children with DCM, Nt-proBNP median values (range) did not change from 32 (5 to 1 777) pmol/l at the start to 35 (3 to 1 302) pmol/l (p=ns) at the end of the study. Only 10% of patients in this cohort were ACEi naïve. In children with CHD, Nt-proBNP levels were lower at the end of the study compared to the beginning. The median Nt-proBNP value at the start of the study were 171 (1 to 2 789) pmol/l and 73 (5 to 2 165) pmol/l (p=ns) at the end. In this cohort 44% of patients were naïve to ACEi treatment.

In patients with DCM, echocardiography (shortening fraction) mean values (±SD)) slightly, but significantly increased in all patients from 22.3% (SD 7.3) to 25.1% (SD 7.8) ($p < 0.05$, t-test) reflecting an improvement of the cardiac conditions of the patients in all age groups. In patients with CHD, shortening fraction remained almost the same during the study period. Mean values (±SD) at the screening and end of study visits were 38.7% (SD 8.6) and 38.5% (SD 6.2) respectively.

In terms of effects on the RAAS, renin, plasma renin activity and angiotensin I, all increased at the end of the two studies compared to pre-dose values. Aldosterone concentrations had decreased at 4 hours after administration of enalapril orodispersible tablets as well as at the end of the study. The observed changes were unlikely to be a consequence of the natural course of disease or maturation-dependent changes of the RAAS system. A comparable trend for the 4 parameters of the RAAS system was observed in ACEi naïve and ACEi pre-treated cohorts, with the main difference being in the baseline pre-dose values. The observed changes in markers of the RAAS during the course of enalapril orodispersible tablets treatment lie within the expected pattern of ACE inhibition.

Data on the use of Aqumeldi in children below 1 month of age in the clinical studies is scarce (n=4).

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 tablet is approximately 60%. Enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor.

The absorption of AQUMELDI orodispersible tablets is not expected to be affected by food.

Distribution

As described in the adult population, over the range of concentrations, which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60%. In adults, the apparent volume of distribution (V/F) of enalapril from AQUMELDI was 93.15 L (SD 33.23 L).

Biotransformation

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

Elimination

Excretion of enalaprilat is primarily renal. In adults, after a single oral dose of enalapril (10 mg), 18% of the administered dose was found in urine and 6% in faeces as unchanged enalapril compared with 43% of enalaprilat in urine and 27% in faeces. Elimination kinetics of enalaprilat is biphasic, with an initial phase reflecting renal filtration (elimination half-life 2 to 6 hours) and a subsequent prolonged phase (terminal elimination half-life 36 hours) which is assumed to represent drug equilibration from ACE enzyme binding sites.

Steady state concentrations of enalaprilat are achieved after 3 or 4 doses of enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%). The elimination half-life for enalapril from

AQUMELDI in adults was 0.77 h (SD 0.11 h) and oral clearance (CL/F) 87.54 l/h (SD 33.45 l/h).

Special populations

Renal impairment

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than 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 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 section 4.2). Enalaprilat may be removed from the general circulation by haemodialysis. The dialysis clearance is 62 ml/min.

Lactation

After a single 20 mg oral dose in five postpartum women the average peak enalapril milk level was 1.7 µg/l (range 0.54 to 5.9 µg/l) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 µg/l (range 1.2 to 2.3 µg/l); peaks occurred at various times over the 24 hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dose.

A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/l 4 hours after a dose and peak enalaprilat levels of 0.75 µg/l about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44 µg/l and 0.63 µg/l of milk respectively.

Enalaprilat milk levels were undetectable (<0.2 µg/l) 4 hours after a single dose of enalapril 5 mg in one mother and 10 mg in two mothers; enalapril levels were not determined.

Paediatric population

In children with DCM, dose and weight normalised maximum plasma concentrations (C_{max}) were 203 ng/ml/mg × kg for enalapril and 155 ng/ml/mg × kg for enalaprilat, with high coefficients of variation of 73% for enalapril and 61% for enalaprilat. Maximum plasma concentrations (T_{max}) were of 1.7 hours for enalapril and 4.6 hours for enalaprilat, after administration of enalapril orodispersible tablet (ODT). In children with CHD, dose and weight normalised maximum plasma concentrations (C_{max}) were 274 ng/ml/mg × kg for enalapril and 178 ng/ml/mg × kg for enalaprilat, with high coefficients of variation of 58% for enalapril and 82% for enalaprilat.

Maximum plasma concentrations (T_{max}) were of 1.8 hours for enalapril and 6.3 hours for enalaprilat, after administration of enalapril ODT.

Data from clinical studies in children with heart failure receiving AQUMELDI allow comparison of the pharmacokinetic parameters in children with DCM and CHD in patients aged 1 month to under 6 years of age (see table below). In this age group, DCM patients showed a 50% lower exposure (AUC) to enalapril, compared to CHD patients. The metabolism of the active metabolite enalaprilat, however, was the same for both groups. The time to achieve maximal concentrations T_{max} of enalapril were similar.

		Enalapril	Enalaprilat	Enalapril	Enalaprilat	Enalapril	Enalaprilat
	n	AUC_{tau}, ss, norm (ng/ml·h/mg·kg)		Cmax, ss, norm (ng/ml/mg·kg)		t-max or tmax, ss (h)	
DCM 1 month to <6 years	20	428.3 (235.5–1338.2)	1040.1 (0–4468.2)	136.4 (44–760.8)	120.4 (0–516.3)	1.99 (0.93–4.17)	5.37 (0–12.02)
CHF 1 month to <6 years	60	785.1	1166.3	261.0	142.1	1.98	6.0
p DCM versus CHD		0.0025	0.4517	0.051	0.9543	0.7632	0.0095

The elimination half life (T½) for enalapril from AQUMELDI in children was 1.67 h and for enalaprilat was 21.66 h.

Although no published results are available describing the PK of enalapril in children with renal impairment, since the drug and its active metabolite are predominantly renally excreted, impaired renal function is expected to result in elevated levels of enalapril and enalaprilat. Thus, the dose of enalapril should be adjusted accordingly and renal function monitored (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats and is not teratogenic. In a study in which female rats were dosed 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 is secreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Crospovidone
Poly(vinyl acetate)
Povidone
Sodium laurilsulfate
Sodium stearyl fumarate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening, use within 100 days.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene bottle with polypropylene cap (equipped with a child-resistant, tamper evident closure system and an integrated silica desiccant) and one scoop to allow extraction of the tablets from the bottle.

AQUMELDI 0.25 mg is provided in bottles of 50, 100 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The first time the bottle is opened, the seal needs to be broken:

- Hold the bottle firmly with one hand.
- With the other hand: push down firmly whilst twisting the cap anti-clockwise.
- Continue turning until the seal is broken.

Due to the small size of the orodispersible tablets, use the scoop provided in the pack to facilitate extraction from the bottle. As much as possible, avoid touching the tablets with your hands.

Administration of doses < 0.25 mg

Where the starting dose is less than 0.25 mg, a lower dose can be achieved by placing one 0.25 mg tablet in a 10 ml oral syringe, adding tap water to the 10 ml graduation, rolling the syringe for 3 minutes to fully disperse the tablet, and administering the required volume to the patient (1 ml will contain 0.025 mg enalapril, 4 mL will contain 0.1 mg enalapril). Sterile water should be used in children under 6 months. After full dispersion of the orodispersible tablet in the oral syringe, the required volume should be used immediately.

Administration via enteral tube

Some patients may require administration via an enteral feeding tube. AQUMELDI rapidly disperses in tap water and can be administered once dispersed. Sterile water should be used in children under 6 months. AQUMELDI should only be dispersed in water by rolling or mixing for 3 minutes in a syringe. A maximum of four orodispersible tablets can be dispersed in 1 ml at any one time. If the child is given

the medicinal product through a feeding tube, flush the tube with at least 3 ml of water after you have given the medicinal product.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51785/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/01/2024

10 DATE OF REVISION OF THE TEXT

16/01/2024