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National Health Care Institute
Research, Development and Medicinal Products
Medicinal Products Team

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Contact
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Our reference:
2025028153

Date: 3 December 2025
Re: GVS advice enalapril (Aqumeldi®) for heart failure in children

Dear Mr Bruijn,

In the letter dated 10 November 2025 (CIBG-25-08921), you asked the National Health Care Institute to perform a substantive review of the medicinal product orodispersible enalapril (Aqumeldi®). The National Health Care Institute recommends the inclusion of orodispersible enalapril in List 1B of the Medicine Reimbursement System (GVS).

In heart failure, the heart stops pumping properly. The heart still works, but it pumps the blood around less vigorously. This reduces the oxygen supply to organs and muscles and can lead to symptoms. These symptoms are shortness of breath, rapid fatigue and fluid retention, leading to swollen ankles, feet or legs. It may also cause babies to drink more slowly or to stop drinking. It can also lead to growth retardation in babies. Part of the treatment for heart failure is the use of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors lower blood pressure.

Registered indication and claim

Aqumeldi® is an orodispersible tablet containing enalapril. This medicinal product is indicated for the treatment of heart failure in children from birth to 18 years. The marketing authorisation holder requests inclusion in List 1B of the Health Insurance Regulation for the above-mentioned indication for children aged 0 to 14 years.

The recommended single starting dose is 0.01 to 0.04 mg/kg (max. 2 mg). This dosage is then increased to 0.15 to 0.3 mg/kg (max. 20 mg) per day in one dose or two divided doses, 8 hours after the initial dose.
The dose should be individualised according to the individual patient's blood pressure, serum creatinine and potassium response.

Interchangeability test Aqumeldi®

Enalapril is one of the ACE inhibitors already included in the GVS on List 1A. This cluster (0C09AAAAO V) contains a number of registered enalapril preparations (tablets of 5, 10 or 20 mg). The registered medicinal product orodispersible enalapril (Aqumeldi®) is, unlike the preparations already mentioned, specifically

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registered for children up to 18 years. The lowest strength of this orodispersible tablet is 20x lower (5 mg vs 0.25 mg) than the lowest strength of the products already available in the GVS.

Despite the fact that orodispersible enalapril (Aqumeldi®) has the same active substance and route of administration as the enalapril preparations mentioned, clustering is not possible due to a difference in age category. Orodispersible enalapril (Aqumeldi®) contains enalapril at a much lower dose. As a result, unlike the other enalapril preparations included in the GVS, this product is intended to be used at a low dose, specifically for children. This is an administration form specifically intended for children.

Interchangeability conclusion
Based on the criteria for interchangeability, the National Health Care Institute concluded that orodispersible enalapril (Aqumeldi®) is *not* interchangeable with other medicinal products included in the GVS. On this basis, orodispersible enalapril (Aqumeldi®) cannot be placed on List 1A. The National Health Care Institute has therefore assessed the possibility of including orodispersible enalapril (Aqumeldi®) in List 1B and concludes that inclusion in List 1B is permitted.

Therapeutic value
ACE inhibitors, including enalapril, have been used for years in the treatment of heart failure in adults. Although there are no Dutch guidelines for paediatric heart failure, the use of ACE inhibitors in children is supported by Dutch physicians treating these children in the academic paediatric heart centres. Enalapril is also included in the paediatric formulary.[1,2]

The European Society of Cardiology guideline contains limited recommendations for children, based on adult evidence and paediatric expertise, with reference to the International Society for Heart and Lung Transplantation ISHLT-Heart Failure Guidelines. This guideline routinely recommends ACE inhibitors in children with heart failure. A European survey among paediatricians shows that there is broad agreement that ACE inhibitors are part of the treatment of children with heart failure, although there is variation in practice.[3] The GIP data show that every year, approximately 1000 children in the Netherlands aged 0 to 14 years use ACE inhibitors. In particular, enalapril oral solution and tablets of enalapril, lisnopril[4]□

The enalapril formulations that have been registered are designed for adults and, in practice, lead to issues when used in children. The available strengths of the active substance are too high and the tablets too large[5] for use by newborns and

[1] Medicine | Enalapril | Paediatric Formulary

[2] https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/e/enalapril#doseringen

[3] Castro Díez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I, Makowski N, et al. Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey. BMJ Paediatrics Open. 2019;3:e000365. https://doi.org/10.1136/bmjpo-2018-000365

[4] Expert-visie mini orodispergeerbare tabletten enalaprilmaleaat (Aqumeldi®) voor de behandeling van hartfalen bij kinderen in Nederland, Namens de afdelingen kindercardiologie van de Academische ziekenhuizen in Nederland: dr. van Osch, dr. Breur, prof. Blom, dr. Fejzic, dr. Du Marchi Sarvaas, dr. Frerich

[5] Tablet 2.5 mg and 5 mg with a diameter of 5 mm, 10 mg with a diameter of 6.5 mm and 20 mg with a diameter of 8.5 mm

younger children. For this group, the magistral suspension of enalapril is reimbursed on the basis of rational pharmacotherapy.

The LENA studies investigated the efficacy and safety of orodispersible enalapril in children with chronic heart failure due to congenital abnormalities or dilated cardiomyopathy. These studies show that the effect of orodispersible enalapril on heart failure, hospitalisation and quality of life is at least as good as current treatment with ACE inhibitors and that treatment with this product is safe. The EMA has assessed orodispersible enalapril (Aqumeldi®) as safe within the prescribed conditions and with good monitoring. Based on the above, The National Health Care Institute concludes that orodispersible enalapril (Aqumeldi®) meets the established medical science and medical practice. Aqumeldi® is therefore eligible for inclusion in List 1B.

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Budget impact analysis
Based on the GIP data, the National Health Care Institute expects that up to 363 children will be eligible for orodispersible enalapril (Aqumeldi®), of which 160 are in the 0–4 age group and 203 are in the 4–14 age group. This estimate is based on the number of users of enalapril oral solution in 2024. The National Health Care Institute assumes that Aqumeldi® will be used mainly in children who are currently being prescribed enalapril oral solution.
In the group 15-18 years, there are up to 27 users of enalapril oral solution, since the GIP database reports 27 users for the age group 15-24 years. These patients are expected to weigh on average more than 53kg (average weight of a 14-year-old) and they would have to take >16 tablets of orodispersible enalapril (Aqumeldi®) per day. In view of this large number of tablets, The National Health Care Institute considers it unlikely that orodispersible enalapril (Aqumeldi®) will be selected for these patients. They can also use the regular tablets, so they only need to take one a day.

The National Health Care Institute estimates the maximum macro-cost at about €2.4 million. For the category 0–4 years, the price per patient per year is assumed to be €2,957, based on the price for a child aged 4 years. The 4-14 year category assumes a price per patient per year of €9,313, based on the price for a 14-year-old child. This is an explicit maximum scenario, as it is calculated using the maximum patient price for each of the two age categories. In practice, a large proportion of patients will receive a lower dose, as they are under 4 or 10 years of age and therefore have a lower weight. In practice, therefore, the price and the macro-cost will be lower.

Cost-effectiveness
The requirement for pharmaco-economic research has been exempted as the macro-cost is expected to remain below 10 million euros.

Should you need any further information, please do not hesitate to contact us.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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