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*2023010543*

**National Health Care Institute**

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**Contact**
K.G. Watson

Date 28 April 2023
Re: GVS advisory report on sacubitril/valsartan (Entresto®)

**Our reference**
2023010543

Dear Mr Kuipers,

In your letter of 27 September 2022 (reference CIBG-22-04456), you asked the National Health Care Institute to assess whether the List 2 condition for the combination preparation sacubitril/valsartan (Entresto®) for patients with symptomatic (NYHA II–IV) chronic heart failure can be extended. The National Health Care Institute has now completed this assessment. The considerations are set out in the attached reports.

**Background**
Sacubitril/valsartan (Entresto®) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker (ARB). Since 2016, it has been included in the Medicine Reimbursement System (GVS) on List 1B. Reimbursement is arranged through a List 2 condition:

> *'Only for an insured person aged eighteen or older with NYHA class II to IV symptomatic chronic heart failure and an ejection fraction ≤ 35%, who is already maintained on a stable dose of an ACE inhibitor/angiotensin II receptor blocker and beta-blocker'*

**Current request**
Based on new clinical data and on a recent amendment to the definition of symptomatic (NYHA II – IV) chronic heart failure with reduced left ventricular ejection fraction (HFrEF; LVEF) in the prevailing European & Dutch treatment guidelines, the marketing authorisation holder has submitted the following request:

- extension of the List 2 condition to include newly diagnosed and ACE inhibitor/angiotensin II receptor blocker (ARB) naive patients, and
- an amendment to the definition of reduced ejection fraction, from ≤ 35% to ≤ 40%.

The National Health Care Institute has established that, since the amendment to the European guideline, the physicians' association is already (has been) using sacubitril/valsartan more broadly in practice than specified by the currently applicable List 2 condition. To avoid situations in which patients with HFrEF who

did not meet the specified condition would have to discontinue treatment with sacubitril/valsartan, thereby exposing them to severe health risks, health care insurers have established a leniency scheme, in consultation with the National Health Care Institute and the physicians' association. The health care insurers will accommodate this situation until the National Health Care Institute has completed its assessment of the marketing authorisation holder's current request.

**Therapeutic value**
Two randomised double-blind trials have directly compared sacubitril/valsartan to enalapril in adults with HFrEF. The PIONEER-HF trial only included patients who were hospitalised for heart failure and who had been stabilised. The study population consisted of two subgroups: patients with HFrEF (LVEF ≤ 40%), who were either newly diagnosed or had not previously been treated with an ACE inhibitor or angiotensin II receptor blocker (ARB). No differences in effectiveness were observed between these subgroups. The PARADIGM-HF trial only included patients with HFrEF (LVEF≤ 35%), who had already been treated with a beta-blocker and an ACE inhibitor or ARB. In the PIONEER-HF trial's study population, the results for cardiovascular mortality, all-cause mortality, and hospitalisation for heart failure were consistent with those previously found in the PARADIGM-HF study. The natural progression of this disease could account for the fact that, following treatment, patients tend to transition relatively rapidly from the acute phase to the stable phase of heart failure. As a result, the long-term effectiveness of sacubitril/valsartan for patients in the PIONEER-HF trial is expected to be about the same as the effectiveness measured in patients in the PARADIGM-HF trial. However, there is considerable uncertainty about the effect of sacubitril/valsartan in outpatients with HFrEF (LVEF ≤ 40%), who were either newly diagnosed or had not previously been treated with an ACE inhibitor or angiotensin II receptor blocker (ARB).

Based on the above criteria, the National Health Care Institute has concluded that, following hospitalisation for heart failure, sacubitril/valsartan has added therapeutic value compared to enalapril in the treatment of adults with symptomatic (NYHA II-IV) chronic heart failure and a reduced left ventricular ejection fraction (LVEF) ≤ 40% (HFrEF) who were either newly diagnosed or had not previously been treated with an ACE inhibitor or angiotensin II receptor blocker (ARB). As such, sacubitril/valsartan complies with established medical science and medical practice in these patients with HFrEF.

At the present time, given the lack of robust scientific evidence, it is not possible to determine the therapeutic value of sacubitril/valsartan relative to enalapril for the above group of patients, if there has been no hospitalisation for heart failure.

**Budget impact analysis**
Taking into account the assumptions surrounding patient numbers, market penetration, and patient compliance, extension of the List 2 condition to include the patient group for which added therapeutic value has been established will be accompanied by additional costs (charged to the pharmaceutical budget) of approximately €1.1 million in the third year. In this analysis, there is a great deal of uncertainty about patient numbers. This can be attributed to ever-changing medical perspectives among general practitioners and cardiologists regarding appropriate heart failure care for this specific, vulnerable patient population.

**National Health Care Institute**

**Date**
28 April 2023

**Our reference**
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## Advice

Based on the above criteria, the National Health Care Institute recommends that you extend the current List 2 condition to include the patient group for which added therapeutic value has been established. We also recommend that patients who are currently undergoing treatment with sacubitril/valsartan under the aforementioned leniency scheme should also qualify for reimbursement. Thus, the new condition is as follows

*'Only for adult insured persons with symptomatic **(NYHA II–IV)** chronic heart failure and a reduced ejection fraction **(LVEF ≤ 40%) (HFrEF),***

- *who are not adequately treated with an ACE inhibitor/angiotensin II receptor blocker (ARB) in combination with a beta-blocker and who are taking this medicinal product as a replacement for the ACE inhibitor/angiotensin II receptor blocker **or***
- *who start taking this medicinal product while hospitalised for heart failure **or***
- *who are already using this drug on 1 August 2023.'*

The National Health Care Institute has discussed this advisory report with the health care insurers and the physicians' association. According to the physicians' association, the majority of outpatients with HFrEF, who – according to the extended List 2 condition – cannot directly start the treatment with sacubitril/valsartan, will still qualify for this sooner rather than later, based on the 'inherently progressive' nature of heart failure. Treatment with sacubitril/valsartan should commence as soon as possible. Any delay would be contrary to the principles of appropriate heart failure care, and would be associated with more hospitalisations (including avoidable hospitalisations) and higher healthcare costs. However, it is not possible to objectively quantify this expectation. Thus, in this context, the National Health Care Institute will monitor sacubitril/valsartan use (and appropriateness) during the upcoming two years, in collaboration with health care insurers and the physicians' association. The National Health Care Institute will discuss with them the advisability of further amending the List 2 conditions, if this is warranted by the evaluation of the outcomes.

Yours sincerely,

Sjaak Wijma
*Chair of the Executive Board*