ENTRESTO (sacubitril/valsartan), a neutral endopeptidase inhibitor in combination with an angiotensin II receptor blocker (ARB)

Minor improvement in patients with class II or III heart failure with LVEF ≤ 35%, remaining symptomatic despite treatment with ACE inhibitor or sartan and requiring a change in treatment.

Main points

ENTRESTO has Marketing Authorisation in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

A modest efficacy was demonstrated versus enalapril 20 mg/day on a composite endpoint of cardiovascular death and hospitalisation for heart failure, in patients with class II or III heart failure according to the NYHA classification with left ventricular ejection fraction (LVEF) ≤ 35% and previously treated and stabilized by ACE inhibitor or sartan.

The adverse effects of ENTRESTO are hypotension, hyperkalemia and impaired renal function.

Therapeutic use

Management of patients with mild, moderate or severe heart failure, with reduced systolic ventricular function (ejection fraction ≤ 40%) combines, in most cases, prescription of:
- a loop diuretic, to relieve symptoms and congestion,
- an angiotensin converting enzyme inhibitor (or an angiotensin II receptor antagonist [ARB] when ACE-inhibitors are poorly tolerated), to reduce the risk of hospitalisation and premature death,
- a digitalis glycoside,
- a beta blocker (bisoprolol, carvedilol, metoprolol or nebivolol) which makes it possible to obtain an additional reduction of mortality and especially of sudden death. Their prescription should be considered in patients with “stable” heart failure.

For patients with stage II and IV heart failure according to the NYHA classification with LVEF ≤ 35% and in whom symptoms persist despite a combination of ACE inhibitor (or ARB when ACE inhibitors are poorly tolerated) and beta-blocker, an aldosterone antagonist (spironolactone or eplerenone) is recommended to reduce the risk of hospitalisation for worsening heart failure and the risk of premature death.

Ivabradine can also be proposed to class II to IV heart failure patients with systolic dysfunction, in sinus rhythm, whose heart rate is ≥ 77 bpm, despite optimised treatment and in whom beta-blockers are contraindicated or poorly tolerated.

Role of the medicinal product in the therapeutic strategy

In light of the results of the PARADIGM-HF study, especially:
- the modest efficacy of the valsartan/sacubitril combination (ENTRESTO) versus enalapril alone, on the occurrence of the first event (death of cardiovascular origin or a first hospitalisation for heart failure, HR=0.80 [0.73; 0.87], p<0.0001) corresponding to an absolute difference in the occurrence of one of these events of 5%,
- but with a highly-selective profile, not very transposable in practice, of the patients included, i.e., stable on ACE inhibitors or sartan,
- and the disputable benefit of offering a change of treatment to patients stabilised on ACE inhibitors or sartan,

ENTRESTO may be offered to patients with class II or III heart failure according to the NYHA classification with LVEF ≤ 35%, previously treated with ACE inhibitor or sartan who remain symptomatic and require a change in treatment.
Clinical data

- In one randomised, double-blind study, versus enalapril 20 mg/day, a significant reduction in the combined primary efficacy endpoint of cardiovascular death or hospitalisation for heart failure, was observed in the valsartan/sacubitril group relative to enalapril: 914 events (21.83%) in the valsartan/sacubitril group versus 1,117 events (26.52%) in the enalapril group: HR=0.80 [0.73; 0.87], p<0.0001 corresponding to an absolute difference of 5%.

- A significant reduction (p<0.0001) of the two components of the primary efficacy endpoint (defined as secondary endpoints) was also observed in the valsartan/sacubitril group versus enalapril:
  - cardiovascular death: HR=0.80 [0.71; 0.89], corresponding to an absolute difference of 3%.
  - hospitalisation for heart failure: HR=0.79 [0.71; 0.89], corresponding to an absolute difference of 3%.

- A significant reduction (p<0.001) of total mortality (secondary endpoint) was also observed in the valsartan/sacubitril group versus enalapril: 711/4,187 deaths (16.98%) versus 835/4,212 (19.82%), HR 0.84 [0.76; 0.93], p=0.005.

- The most commonly reported adverse effects during treatment with ENTRESTO were hypotension, hyperkalemia and impaired renal function.

Benefit of the medicinal product

- The actual clinical benefit* of ENTRESTO is substantial in patients with class II or III heart failure according to the NYHA classification with LVEF ≤ 35%, who remain symptomatic despite treatment with ACE inhibitor or sartan and require a change in treatment.

- ENTRESTO provides a minor clinical added value** (CAV IV) in these patients.

- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

---

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

This document was created on the basis of the Transparency Committee Opinion of 11 May 2016 (CT-14835) available at www.has-sante.fr

© Haute Autorité de Santé 2016