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SACUBITRIL / VALSARTAN

▼ENTRESTO-NEPARVIS® FOR HEART FAILURE

DRUG ASSESSMENT REPORT
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DTB_Navarre

Useful for your heart if you use your head

Indications

Chronic symptomatic heart failure (HF) with reduced left ventricular ejection fraction (LVEF).

Mechanism of action

Neprilysin inhibition increases the activity of natriuretic peptides and other vasoactive peptides, but it also elevates angiotensin II, which requires the administration of an ARB.

Dosage and administration

Oral administration as ACE inhibitor or ARB replacement. The recommended initial dose is 49 mg/51 mg twice a day. At 2-4 weeks, the dose is doubled to 97 mg/103 mg twice a day. The dose can be adjusted according to patient's tolerability. The dose must be titrated according to previous ACE inhibitor/ARB dosage, systolic blood pressure (if SBP 100 to 110 mmHg the initial dose is 24/26) and the presence of moderate renal/liver failure.

Clinical efficacy

Marketing authorization is based on data from the PARADIGM-HF trial, which was stopped at 3.5 years, after a median follow-up of 2.25 years. The trial revealed that SAC/VAL (97/103mg/12h), as compared to enalapril 10 mg/12h, reduced by 4.7% the absolute risk for hospitalization for HF or cardiovascular death, NNT=21 (15 to 35). It also reduced CV mortality by 3.2%, NNT=31 (22 to 63), all-cause mortality by 2.8%, NNT=36 (23 to 93), and hospitalization due to HF by 2.8% NNT= 36 (24 to 77) in patients with reduced ejection heart failure (REHF) with elevated plasma BNP (≥150 pg/mL) or NT-pro-BNP (≥600 pg/mL) levels who, despite receiving the optimal treatment recommended, showed symptoms of HF (NYHA II-III and IV class).

Patients most likely to benefit from the treatment and with a lower risk of experiencing adverse events were selected. A total of 42% of patients were excluded during the screening phase (62% due to low levels of natriuretic peptides and 38% due to hypotension, renal failure, liver failure, etc.). Next, during the pre-randomization phase, drop-outs due to intolerance to treatment exceeded 20%. Finally, 47% (n=8.442) of the 18,071 patients initially recruited were included in the double-blind comparison phase.

The effectiveness of SAC/VAL in clinical practice will be probably lower than the one reported in the PARADIGM-HF trial for the following reasons:

- The trial was stopped early and this could have overestimated the real effect of SAC/VAL.
- Patients who did not tolerate enalapril or SAC/VAL (20% approx.) were excluded during the pre-randomization phase, mainly due to hypotension and high blood potasium levels. Sensitivity analyses to assess the impact of the 2,085 drop-outs during the preinclusion phase revealed that the relative risk reduction would be reduced from 20% to 15-16%.

Provides benefit when optimal therapy with ACE inhibitors or ARBs is not effective

- Doctors were not allowed to use enalapril at full doses (40mg daily). However, the mean dose in the SAC/VAL group reached 300±57 mg of valsartan, which exceeds the dose used in clinical practice.
- During the trial, 14% and 7% of patients had been treated with a defibrillator / implantable cardioverter (ICD) or with bi-ventricular pacing, respectively, but the use of these devices in clinical practice in Europe is two-fold higher. These devices have been proven to reduce death and disability in patients with heart failure with reduced ejection fraction (REF-HF). Whether access to these devices would have mitigated treatment benefits is unknown.

Other concerns on the applicability of results to other patients include:

- Patients with HF NYHA class IV were underrespresented (0.7%). Most patients were class II (70,5%) a quarter of them class-III (24%).

ABSTRACT

Sacubitril/Valsartan (SAC/VAL) is a fixed-dose combination of a neprilysin inhibitor and an ARB.

SAC/VAL has been proven to provide clinical benefit in terms of morbidity and mortality in patients who experienced heart failure (HF) with ejection fraction ≤35% and increased BNP or NT-pro-BNP plasma levels which symptoms are not controlled with the optimal therapy recommended.

Associated risks include: hypotension, hyperkalemia and angioedema. There is a potential risk for cognitive impairment in the long term.

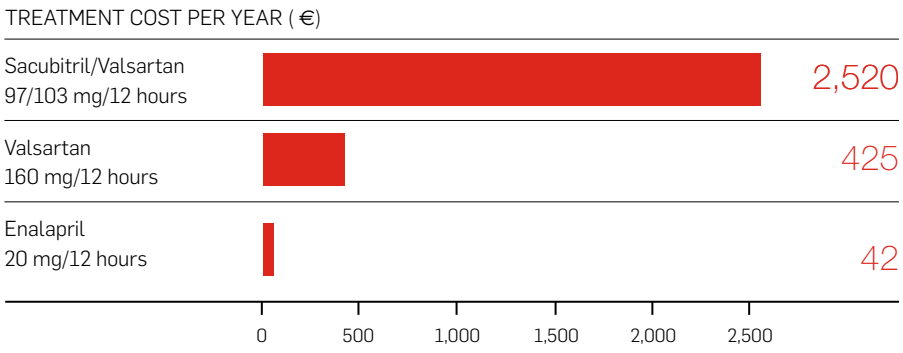
SAC/VAL must be only used in patients with similar characteristics to those of study patients, as its effectiveness and safety has only been demonstrated in this group of patients.

Treatment/year cost per patient amounts to €2,520, 60-fold higher than enalapril.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	**SOME ADDED VALUE IN SPECIFIC SITUATIONS**
1	NO THERAPEUTIC INNOVATION
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



· The mean age of patients was 64 years (±11 years). Patients older than 75 years were underrepresented (18%) and subgroup analysis yielded no significant differences in this group in terms of efficacy.

Safety

Adverse reactions

As compared to enalapril, SAC/VAL involves a higher risk for hypotension (17.6% vs 11.97%), clinically relevant systolic blood pressure reduction (4.76% vs 2.67%), and angioedema (0.5% vs 0.2%), and a lower risk for renal failure (10.1% vs 11.5%) and hyperkalemia (11.6% vs 14.0%). Given that patients in the PARADIGM-HF trial were highly selected through a run-in period before randomization, the incidence of adverse reactions in real practice is expected to be higher, which makes it difficult to establish the risk/benefit balance of the drug.

Contraindications

Concomitant use of ACE inhibitors or ARB
A history of angioedema related to previous treatment with ACE inhibitors or ARB (SAC/VAL therapy must not be initiated until 36 hours after therapy with ACE inhibitors is discontinued).
Hereditary or idiopatic angioedema.
Do not initiate if potasium levels are >5.4 mmol/l or SBP <100 mmHg.
Concomitant use of aliskiren in patients with diabetes mellitus or renal failure.

Warnings and precautions

Renal function (serum creatinine, ClCr, BUN, proteinuria), blood pressure and potassium levels must be monitored.

Usage in special situations

Pediatric patients: There are no data on the safety and effectiveness of SAC/VAL in patients aged < 18 years. **Renal failure:** Dose adjustment is not required in patients with mild to moderate renal failure. The initial dose in patients with moderate renal failure is 24 mg/26 mg twice a day. No data is available for severe renal failure. **Liver failure.** Dose adjustment is not required in patients with mild liver failure. Experience in patients with moderate liver failure or AST/ALT values doubling the upper cut-off point is limited. The initial dose is 24mg/26mg twice a day. Contraindicated in patients with severe liver failure, biliary cirrhosis or cholestasis. **Pregnancy and lactation.** No data available.

Drug-to-drug interactions

Association with PDE5 inhibitors (eg. sildenafil) increases the risk for hypotension.
Possible reduction of plasma metformin and furosemide levels.
Increased plasma levels of drugs such as bosentan, statins, fexofenadine or meglitinides (eg nateglinide).
Possible increase in serum lithium levels.
NSAIDs and acetylsalicylic acid can impair renal function.
Concomitant use of potassium-sparing diuretics, potassium supplements, and mineralocorticoid antagonists may increase potassium and serum creatinine levels.

Risk Management Plan

Neprilysin inhibition by sacubitril may block beta amyloid degradation, which is related to the pathogenesis and progression of Alzheimer's disease. The clinical effects of sacubitril –especially in the long term– are unknown.

Place in therapeutics

Drug therapy for heart failure with reduced ejection fraction (REF-HF) includes ACE inhibitors to block the renin-angiotensin-aldosterone system in combination with beta-blockers and/or aldosterone antagonists. ACE inhibitors and beta-blockers have been proven to reduce mortality rates by 10-20% as compared to placebo in several clinical trials including different patients with REF-HF. However, evidence of the benefit of ARBs on mortality in patients with HF is inconsistent and it is recommended only for patients with intolerance to ACE inhibitors.
Aldosterone antagonists have demonstrated to reduce overall mortality by 25-30% in patients with HF with LVEF ≤35% and symptoms of NYHA class II-IV on treatment with the recommended drug therapy.

The Pharmacy Central Committee of the Navarre Health Service determined that SAC/VAL must only be used **in a specific group of patients** meeting the following four criteria:

1. LVEF<35%.
2. Elevated BNP o NT-pro BNP levels.
3. Symptomatic Heart Failure NYHA class II-III.
4. On treatment at maximum dose of ACE inhibitors or ARB + beta-blockers and aldosterone antagonists (except in case of intolerance or contraindication).

Presentations

Entresto® (Novartis), Neparvis® (Rovi) 28 film-coated tablets, 24/26mg (109.28€), 49/51mg (193.35€), 97/103mg (193.35€).

References

Based on the evaluation report on sacubitril/valsartan: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm

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