

Sacubitril/valsartan (ENTRESTO™)

Summary & Practical Tips

Sacubitril/valsartan is an angiotensin II receptor blocker neprilysin inhibitor (ARNI) - a unique compound that includes two active moieties: valsartan (angiotensin II receptor blocker [ARB]) and sacubitril (neprilysin inhibitor).

Mechanism of action:

Sacubitril is a neprilysin inhibitor – an enzyme that prevents the degradation of natriuretic peptides (NPs)

Neprilysin inhibition increases the concentration of NPs, neurohormones which have potent natriuretic (↑sodium loss) and vasodilatory properties as well as antihypertrophic and antiproliferative (↓ myocardial hypertrophy and ventricular remodelling) effects. NPs counteract the deleterious effects of the Renin-Angiotensin-Aldosterone (RAAS) system and reduce sympathetic drive.

Valsartan is an ARB which blocks the hormone angiotensin II from binding to its receptor thus preventing vasoconstriction, release of other hormones such as aldosterone and vasopressin, and decreasing myocardial fibrosis and hypertrophy.

PARADIGM-HF:

In this Trial sacubitril/valsartan reduced the risk of cardiovascular death and hospitalization among patients with chronic heart failure (HF) (NYHA Class II-IV) and a left ventricular ejection fraction of ≤ 40% despite optimally tolerated guideline driven heart failure therapies.

The number needed to treat (NNT) with sacubitril/valsartan to prevent one cardiovascular death or HF hospitalization was 21 patients over a 27 month period.

The relative risk reduction (RRR) for cardiovascular death or first heart failure hospitalization was 21% with an absolute risk reduction (ARR) of 4.6% when a patient was treated for 27 months.

Cost- \$7.80 per day= \$240 per month- not currently covered by Fair PharmaCare BC

Indications for Usage

Canadian Cardiovascular Society HF 2014 Guidelines- [http://www.onlinecjc.ca/article/S0828-282X\(14\)01492-5/pdf](http://www.onlinecjc.ca/article/S0828-282X(14)01492-5/pdf)

GPAC- Guidelines – <http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/heart-failure-chronic>

Do NOT use sacubitril/valsartan concomitantly with an ACE-I or ARB

Sacubitril/valsartan requires careful monitoring and titration.

Initiation of this medication should only be undertaken by physicians or nurse practitioners experienced in the treatment of HF

Prescribing tips:

Sacubitril/valsartan is NOT to be used as a first line treatment for heart failure

Sacubitril/valsartan may be considered *instead of* an Angiotensin Converting Enzyme Inhibitor (ACE-I) or ARB in patients with:

- ✓ NYHA II-III functional status.
- ✓ LVEF \leq 40% (preferably measured within the last year) despite a trial of optimally tolerated doses of guideline driven heart failure therapy including ACE-I, ARB, Beta Blocker (BB) and Mineralocorticoid Receptor Antagonists (MRA) for a minimum of three months (based on the potential for improvement on standard medical therapy) .
- ✓ Elevated BNP \geq 150 pg/mL or NT-proBNP \geq 600 pg/mL at time of decision to switch, or/and a heart failure hospitalization within the last year.
- Consider decreasing the patient's diuretic dose for 3-4 days when initiating sacubitril/valsartan to reduce the risk of hypotension and kidney injury.
- NT-pro BNP is the biomarker of choice to be used once sacubitril/valsartan has been started, as BNP measurements will be inaccurate.
- Consider starting at the lowest dose of sacubitril/valsartan (24 mg sacubitril / 26 mg valsartan) in patients who have risk factors for hypotension or low baseline systolic blood pressure, in patients' \geq 75 years of age.
- Patients with moderate hepatic impairment (Child-Pugh B classification) should be initiated on the lowest dose of sacubitril/valsartan.
- Sacubitril/valsartan doses lower than 97/103mg po BID have not yet been shown to reduce morbidity and mortality. Every effort should be made to reach target dose.

Prescribing CAUTIONS:

- **A 36 hour wash out period is required when switching from an ACE-I to sacubitril/valsartan.**
- Sacubitril/valsartan can cause hypotension, potassium and renal abnormalities.
- Sacubitril/valsartan may increase statin levels (especially simvastatin & atorvastatin). Careful monitoring for statin toxicity is recommended.
- Concomitant use of sacubitril/valsartan with aliskiren (Rasilez™) containing drugs should be avoided.
- Theoretically, patients on sacubitril/valsartan could be at risk of Alzheimer's disease, as amyloid β is a substrate for neprilysin. This will be addressed in ongoing cognitive studies.
- DO NOT use during pregnancy or if breast feeding.