ARNI (Angiotensin Receptor-Neprilysin Inhibitor)

**INTRODUCTION**

Angiotensin receptor-neprilysin inhibitor (ARNI) is indicated in adults with NYHA Class II to IV chronic heart failure (HF) and reduced ejection fraction (HFrEF) to reduce the risks of hospitalization for HF and cardiovascular (CV) death. Normally used along with other therapies for HF, in place of an ACE inhibitor (ACE-I) or other angiotensin receptor blocker (ARB). Superiority was shown in comparison with enalapril for the risk of the composite endpoint of death from CV causes or hospitalization for HF [1]. As per ACC/AHA/HFSA recommended that ARNI replace an ACE-I or ARB in selected patients with chronic symptomatic HFrEF (NYHA class II/III) who have an adequate blood pressure and are already tolerating a reasonable dose of ACE-I or ARB [2].

**EXCLUSION CRITERIA/CONTRAINDICATIONS**

- Angioedema related to previous ACE-I or ARB therapy or regardless of cause
- Pregnancy/breastfeeding
- Severe hepatic impairment (Child-Pugh C classification)
- Hypersensitivity to any component
- **Avoid concomitant use with:**
  - ACE-I (due to increased risk of angioedema). Do NOT administer within 36 hours of switching to or from an ACE-I
  - Aliskiren (Tekturna®) in patients with Diabetes. Also, avoid use of Sacubitril/Valsartan with Aliskiren in patients with GFR<60mL/min
  - Other ARBs (avoid dual ARB therapy)

**AVAILABLE AGENTS**

- Entresto® [Sacubitril 24mg/Valsartan 26mg, Sacubitril 49mg/Valsartan 51mg, Sacubitril 97mg/Valsartan 103mg tablets]

**DOsing/Administration & Titration Algorithm**

- **NOTE:** ARNI should not be administered concomitantly with ACE-I or ARB, nor within 36 hours of switching from or to an ACE-I

<table>
<thead>
<tr>
<th>Sacubitril-Valsartan (Entresto®)</th>
<th>Initial Dose (not currently taking ACE-I or ARB, or taking low doses): Sacubitril 24mg/Valsartan 26mg orally twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Dose (switching from an ACE-I or ARB at a standard dosage): Sacubitril 49mg/Valsartan 51mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>Maintenance Dose: Double the dose every 2 to 4 weeks to a target dosage of Sacubitril 97mg/Valsartan 103mg twice daily, as tolerated</td>
</tr>
</tbody>
</table>
ASSESSMENT PRIOR TO DOSE INCREASE

- SBP>80mmHg
- Renal Function
- K⁺ <5.5mEq/L
- Urine Output

ARB Dose Equivalencies:

- As noted in the prescribing information for the Sacubitril-Valsartan combination tablet, the Valsartan in this combination tablet is more bioavailable than the Valsartan in other marketed tablet formulations. Table below shows Valsartan doses in the combination tablet and the equivalent doses of Valsartan in other marketed tablet formulations:

<table>
<thead>
<tr>
<th>Sacubitril-Valsartan combination tablet</th>
<th>Valsartan tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>26mg</td>
<td>40mg</td>
</tr>
<tr>
<td>51mg</td>
<td>80mg</td>
</tr>
<tr>
<td>103mg</td>
<td>160mg</td>
</tr>
</tbody>
</table>

RENAL DOSE ADJUSTMENT

- GFR>30mL/min: No Dosage adjustment necessary
- GFR<30mL/min: Initiate with Sacubitril 24mg/Valsartan 26mg twice daily

HEPATIC DOSE ADJUSTMENT

- Mild Impairment (Child-Pugh class A): No dosage adjustment necessary
- Moderate Impairment (Child-Pugh class B): Initiate with Sacubitril 24mg/Valsartan 26mg twice daily
- Severe Impairment (Child-Pugh class C): Use NOT recommended

CONSIDERATIONS

- Monitor at Baseline and periodically:
  - Serum Potassium, renal function and BP
  - Closely monitor patients with low serum sodium, diabetes mellitus, SBP<80mmHG and impaired renal function
- Uptitrate every 2 to 4 weeks as recommended except when limited by BP
- **NOTE**: Sacubitril/Valsartan has been shown to lower BP more than ACE-I. If appropriate, a reduction in loop diuretics should be considered in patients who are euolemic.
  - (Reduction in diuretics parallels what should be done with ACEI or ARB’s in euolemic patients.)
  - (Note that the population of the PARADIGM trial was outpatient. The drug has not been adequately tested in the inpatient population.)
- Titrate to maximum tolerated dose or target dose
- Store in original package
- For those patients for whom and ARNI is not appropriate, continued use of an ACE-I for all classes of HFrEF remains strongly advised
- For those patients for whom an ACE-I or ARNI is inappropriate, use of an ARB remains advised
REFERENCES:


[3] UpToDate: Use of angiotensin II receptor blocker and neprilysin inhibitor in heart failure with reduced ejection fraction
