Initiation, Titration and Monitoring Recommendations for Sacubitril/Valsartan (ENTRESTOTM) Usage in British Columbia

Patient must meet all the British Columbia eligibility criteria prior to initiating Sacubitril/Valsartan

Sacubitril/Valsartan is NOT to be used as first line therapy for HFrEF- (≤ 40%).

Consider initiating Sacubitril/Valsartan ONLY AFTER patient established on guideline-directed triple medical therapy for HF-rEF including Angiotensin Converting Enzyme Inhibitor (ACE-I), Angiotensin II Receptor Blocker (ARB), Beta Blocker (BB), Mineralocorticoid Receptor Antagonist (MRA) for a minimum of 3 months (based on the potential for improvement on standard medical therapy)

Prescribing tips
Sacubitril/Valsartan may be considered instead of an ACE-I or ARB in patients with:

- NYHA II-III functional status.
- LVEF ≤ 40% (preferably measured within the last year) despite a trial of optimally tolerated doses of guideline driven heart failure therapy including ACE-I/ARB, BB and MRA for a minimum of three months,(based on the potential for improvement on standard medical therapy).
- Elevated BNP > 150 pg/mL or NT-proBNP ≥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 (24.3 mg sacubitril / 25.7 mg valsartan) in patients who have risk factors for hypotension or low baseline systolic blood pressure and in patients’ ≥ 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 97.2/102.8mg po BID have not yet been shown to reduce morbidity and mortality. Every effort should be made to reach target dose.

Prescribing CAUTIONS:
When converting from ACE-I, a 36 hour wash out period is required before Sacubitril/Valsartan can be started

- 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.

Ordering sacubitril/valsartan (Entresto™):

<table>
<thead>
<tr>
<th>Sacubitril/valsartan must be ordered using available strengths as below:</th>
<th>Actual Content (Sacubitril/Valsartan)</th>
<th>Referred to in clinical studies as:</th>
<th>Equivalent Diovan™ dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>sacubitril/valsartan 24/26 BID (White pill)</td>
<td>24.3mg / 25.7mg</td>
<td>50mg BID</td>
<td>40mg BID</td>
</tr>
<tr>
<td>sacubitril/valsartan 49/51 BID (yellow pill)</td>
<td>48.6 mg / 51.4 mg</td>
<td>100mg BID</td>
<td>80mg BID</td>
</tr>
<tr>
<td>sacubitril/valsartan 97/103 BID (pink pill)</td>
<td>97.3 mg / 102.8mg</td>
<td>200mg BID</td>
<td>160mg BID</td>
</tr>
</tbody>
</table>
**Titration Algorithm**

### Assess

Eligibility Checklist Completed
- Patient on guideline directed ACE-I or ARB at optimally tolerated dose
  - if not, titrate to optimally tolerated dose and reassess eligibility for sacubitril/valsartan in 3 months

### Washout

If on ACE-I, **STOP for 36 hours** to reduce the risk of angioedema

*Do not need to stop ARB 36 hours prior to starting sacubitril/valsartan*

### Initiate

- **Initiate sacubitril/valsartan 49/51mg BID** - if patient at target ACE-I or ARB* dose
- **Initiate sacubitril/valsartan 24/26mg BID** - if patient on less than target dose ACE ARB,* older than 75 years old, at risk for hypotension, have moderate hepatic impairment or clinician concern about drug intolerability

### Titrate

Increase to next highest dose every 2-4 weeks to a target dose of 97/103mg BID
- sacubitril/valsartan 24/26 mg po BID
- sacubitril/valsartan 49/51 mg po BID
- sacubitril/valsartan 97/103mg po BID

### Monitor

**SCr, K⁺ and blood pressure**

1 week after initiation, after each dose increase and with each practitioner visit

Consider assessment of LV Function only if it will alter treatment or if otherwise clinically indicated

### Reassess

**Consider decreasing or stopping sacubitril/valsartan if:**
- SCr increases by > 30%
- K⁺ is greater than 5.4 mmol/L
- Symptomatic hypotension (< 95 mmHg)
  - *36 hour washout of sacubitril/valsartan is required if switching back to ACE-I*

### Target Daily Dose

<table>
<thead>
<tr>
<th>ACE-I</th>
<th>ARB</th>
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<tbody>
<tr>
<td>captopril 150mg</td>
<td>valsartan 320mg</td>
</tr>
<tr>
<td>enalapril 20mg</td>
<td>candesartan 32mg</td>
</tr>
<tr>
<td>perindopril 8mg</td>
<td></td>
</tr>
<tr>
<td>ramipril 10mg</td>
<td></td>
</tr>
<tr>
<td>trandolapril 4mg</td>
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