Initiation, Titration and Monitoring Recommendations for sacubitril/valsartan (ENTRESTO™) 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 mg sacubitril / 26 mg valsartan) in patients who have risk factors for hypotension or low baseline systolic blood pressure and in patient’s ≥ 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:
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 breastfeeding.

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>24mg / 26mg</td>
<td>50mg BID</td>
<td>40mg BID</td>
</tr>
<tr>
<td>sacubitril/valsartan 49/51 BID (yellow pill)</td>
<td>49 mg / 51 mg</td>
<td>100mg BID</td>
<td>80mg BID</td>
</tr>
<tr>
<td>sacubitril/valsartan 97/103 BID (pink pill)</td>
<td>97 mg / 103mg</td>
<td>200mg BID</td>
<td>160mg BID</td>
</tr>
</tbody>
</table>

Final April 2016 updated September 2016
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 mg / 51 mg BID - if patient at target ACE-I or ARB* dose
- Initiate sacubitril/valsartan 24mg /26mg BID - if patient on less than target dose ACE-I or ARB,* older than 75 years old, risk factors for hypotension, has 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 24mg / 26mg po BID
  - sacubitril/valsartan 49 mg / 51 mg po BID
  - sacubitril/valsartan 97 mg /103mg po BID

Monitor
- Serum creatinine (Scr), potassium (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 greater than 30% * 36 hour washout of sacubitril/valsartan is required if switching back to ACE-I*
  - K+ is greater than 5.4 mmol/L
  - Symptomatic hypotension ( < 95 mmHg)

<table>
<thead>
<tr>
<th>*Target Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
</tr>
<tr>
<td>captopril 150mg</td>
</tr>
<tr>
<td>enalapril 20mg</td>
</tr>
<tr>
<td>perindopril 8mg</td>
</tr>
<tr>
<td>ramipril 10mg</td>
</tr>
<tr>
<td>trandolapril 4mg</td>
</tr>
</tbody>
</table>

Final April 2016 updated September 2016