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# PHARMACY AND THERAPEUTICS NEWSLETTER

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## In This Issue...



## Changes to Formulary

### Additions

**1. Sacubitril-Valsartan 24 mg-26 mg, 49 mg-51 mg, 97 mg-103 mg tablets (Entresto®)**

- Angiotensin receptor-neprilysin inhibitor (ARNI) used to treat heart failure with reduced ejection fraction
- Restricted to cardiologists or internal medicine specialists, unless on this medication prior to admission
- See pages 1-2 for drug review

**2. Varenicline 0.5 mg, 1 mg tablets (Champix®)**

- Partial nicotine agonist, smoking cessation aid

**3. Olopatadine 0.1% ophthalmic drops (Patanol®)**

- Histamine $H_1$ antagonist eye drop

**4. Plerixafor 20 mg/mL injection (Mozobil®)**

- Hematopoietic agent (stem cell mobilizer)
- Restricted to indications outlined in the BCCA Benefit Drug List AND patients who are registered with BCCA

## Updated Policies

**1. LIPID EMULSION 20% (SMOFlipid®) - REMOVAL OF RESTRICTION**

In 2016, SMOFlipid® emulsion was added to formulary as an alternate source of calories and omega-3 fatty acids for patients requiring parenteral nutrition. At VA, it was further restricted to review by the parenteral nutrition pharmacist. This restriction was in place to ensure appropriateness and limit administration costs due to the more costly DEHP-free tubing required for its administration. All tubing for the new Alaris Smart Pumps is now DEHP-free, and thus extra tubing for SMOFlipid® is no longer required. As a result, the SMOFlipid® restriction has been removed.

## New Drug/Drug Products

**SACUBITRIL/VALSARTAN (ENTRESTO®)**

Will Shum, B.Sc. (Pharm), ACPR, Elaine Lum, Pharm.D., ACPR

Sacubitril/valsartan is a combination product belonging to a class of medications known as angiotensin receptor-neprilysin inhibitors (ARNI). It is used to treat heart failure with reduced ejection fraction (HFrEF).

*Mechanism of Action*

Sacubitril inhibits neprilysin, a neutral endopeptidase, that degrades endogenous vasoactive peptides, including natriuretic peptides (such as brain natriuretic peptide [BNP] and atrial natriuretic peptide [ANP]), bradykinin, and adrenomedullin.[1,2] Raising the level of natriuretic peptides is thought to have positive effects in HFrEF through vasodilation, natriuresis and diuresis, inhibition of renin and aldosterone release, and inhibition of fibrosis.[2,3] However, because sacubitril also prevents the breakdown of angiotensin II (ATII), an ATII receptor blocker (ARB) is necessary to counteract the adverse effects of elevated ATII levels. ARBs block the

renin-angiotensin-aldosterone system, preventing sodium and water retention, vasoconstriction, hypertrophy, and fibrosis.[3]

*Evidence/Place in Therapy*

The PARADIGM-HF study compared sacubitril-valsartan against enalapril in a prospective, randomized double-blind trial of 8442 patients with HFrEF (EF≤35%, NYHA II-IV).[4] The majority of patients were classified as NYHA II or III. Sacubitril-valsartan significantly reduced the primary composite outcome of cardiovascular mortality or first hospitalization for heart failure, as well as the secondary outcome of all-cause mortality (Table 1). Sacubitril-valsartan was generally well tolerated, other than having a higher rate of symptomatic hypotension. However, it should be noted that a trial run-in period excluded patients who were intolerant to either sacubitril or valsartan.

The current 2017 Canadian Cardiovascular Society guidelines for heart failure recommend that "an ARNI be used in place of an angiotensin-converting-enzyme inhibitor (ACEI) or ARB, in patients with HFrEF who remain symptomatic despite treatment with appropriate doses of guideline-directed medical therapy [i.e. triple therapy with beta-blocker, ACEI/ ARB, and mineralocorticoid receptor antagonist (MRA) such as spironolactone]".[5]

*Dosage*

Sacubitril-valsartan dosing should specify both components of the drug (e.g. sacubitril-valsartan 24 mg-26 mg po BID). Patients who were previously on a low dose of ACEI (≤ 10 mg/day of enalapril or equivalent) or ARB (≤ 160 mg/day of valsartan or equivalent) should be initiated on sacubitril-valsartan at 24 mg-26 mg PO BID. Patients who were previously on doses of ACEI or ARB higher than those stated above should be initiated on sacubitril-valsartan at 49 mg-51 mg PO BID.[6] The dose should be doubled as tolerated every 2 to 4 weeks until a target dose of sacubitril-valsartan 97 mg-103 mg PO BID is achieved. Use with an ACEI is contraindicated due to risk of angioedema from excess bradykinin levels. A 36-hour washout period is required when switching to or from an ACEI. Sacubitril-valsartan is not recommended in patients with severe renal impairment (eGFR < 30 mL/ min/1.73 m2 ) due to lack of data.[4]

*Monitoring*

Patients on ARNI should be monitored for hypotension, renal function, hyperkalemia, and angioedema. When assessing heart failure, NT-proBNP levels should be measured rather than BNP levels since sacubitril inhibits the breakdown of BNP and thus will be elevated.

*Restrictions/Pharmacare Special Authority*

At VA, initiation of treatment with sacubitril-valsartan is restricted to cardiologists or internal medicine specialists.

BC Pharmacare Special Authority is available for patients who meet the following criteria:

1) LVEF less than 40%,
2) NYHA II to III, and
3) Persistent symptoms despite ≥ 4 weeks of optimum stable doses of ACEI/ARB, beta blocker, and MRA.

*References*


1. Drazner M. Use of angiotensin receptor-neprilysin inhibitor in heart failure with reduced ejection fraction. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2017.
2. ENTRESTO (sacubitril/valsartan) Product Monograph [Internet]. Dorval: Novartis Pharmaceuticals Canada Inc.; 2017.
3. ENTRESTO (sacubitril/valsartan) tablets—Mechanism of Action [Internet]. Entrestohcp.com. 2018 [cited 7 June 2018]. Available from: https://www.entrestohcp.com/mechanism-of-action
4. McMurray J, Packer M, Desai A, Gong J, Lefkowitz M, Rizkala A *et al*. Angiotensin–neprilysin inhibition versus enalapril in heart failure (PARADIGM-HF). NEJM 2014;371(11):993-1004.
5. Ezekowitz J, O'Meara E, McDonald M, Abrams H, Chan M, Ducharme A *et al.* 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33(11):1342-1433.


**Table 1. Outcomes from PARADIGM-HF trial[4]**

| | Sacubitril-Valsartan (N=4187) | Enalapril (N=4212) | Hazard Ratio or Difference (95% CI) | P-value |
|---|---|---|---|---|
| **Primary Outcome (%)** | | | | |
| Death from cardiovascular causes or first hospitalization for worsening heart failure | 914 (21.8) | 1117 (26.5) | 0.80 (0.73-87) | <0.001 |
| **Secondary Outcomes (%)** | | | | |
| Death from cardiovascular causes | 558 (13.3) | 693 (16.5) | 0.80 (0.71-0.89) | <0.001 |
| First hospitalization for worsening heart failure | 537 (12.8) | 658 (15.6) | 0.79 (0.71-0.89) | <0.001 |
| Death from any cause | 711 (17.0) | 835 (19.8) | 0.84 (0.76-0.93) | <0.001 |