MEDICAL ARTS PHARMACY

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Health Matters

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New Entresto shows benefit over standard treatment for chronic heart failure

In a study involving over 8,400 patients, which according to Health Canada is the largest clinical trial in heart failure ever conducted, Entresto, a fixed-dose combination of sacubitril and valsartan, demonstrated:

- *Reduced risk of death from cardiovascular causes by 20%*
- *Reduced heart failure hospitalizations by 21%*
- *Reduced risk of all-cause mortality by 16%*

The primary objective of the study was to determine whether Entresto is superior to ACE inhibitor enalapril, and formed the basis on which Health Canada approved Entrestro in October 2015.

Chronic heart failure is a major cause of morbidity and mortality in Canada, and about 600,000 Canadians currently suffer from the condition. Additionally, there are about 50,000 new cases of chronic heart failure diagnosed annually in Canada.

New Class

Sacubitril belongs to a new class of medications called Neprilysin Inhibitor, and is indicated for the treatment of heart failure. Neprilysin (or neutral endopeptidase) is an enzyme responsible for the breakdown of Natriuretic Peptides (NPs), which are involved in regulating sodium and water balance, blood volume and arterial pressure.

There are two main NPs involved: Atrial natriuretic peptide (ANP) and Brain-Type natriuretic peptide (BNP). These peptides are increased in response to a fluid overload state, such as heart failure. NPs directly dilate veins and thereby decrease central venous pressure, which reduces cardiac output by decreasing ventricular preload. NPs also dilate arteries, which decreases systemic vascular resistance and systemic arterial pressure.

NPs affect the kidneys by increasing glomerular filtration rate and filtration fraction, which produces natriuresis and diuresis. These renal effects of NPs are potassium sparing unlike most diuretic drugs. They also decrease renin release, thereby decreasing circulating levels of angiotensin II and aldosterone. Taken together, these NPs decrease blood volume, arterial pressure, central venous pressure, and cardiac output.

Sacubitril inhibits Neprilysin causing an avoidance of NPs breakdown

Entresto

DOSAGE FORMS	• Initial: 48.6/51.4mg twice daily. Increase the dose as tolerated every 2 to 4 weeks to the target dose of 97.2/102.8mg twice daily. • Patients with risk factors for hypotension or low systolic blood pressure: Consider 24.3/25.7mg twice daily and titrate as described above. • **Patients currently using an ACE-I: Stop ACE-I and observe 36 hour washout period before starting Entresto** • ≥ 75 years old: 24.3/25.7mg twice daily and titrate as above. • eGFR < 30ml/min/1.73m^2: Use not recommended. • Moderate Hepatic Impairment: Initial 24.3/25.7mg twice daily. • Severe Hepatic Impairment: Use not recommended
ADVERSE REACTIONS	Hypotension, Hyperkalemia, Increased creatinine, Orthostatic hypotension, Dizziness, Angioedema, Renal Failure, Cough
CONTRA-INDICATIONS	History of angioedema, Use of aliskiren, Use of ACE-I
REMARKS	Please take note that the valsartan in Entresto is more bioavailable than other marketed valsartan (26mg=40mg, 51mg=80mg, 103mg=160mg)