MAZANKOWSKI
ALBERTA HEART INSTITUTE

November 2015

LCZ696 (Sacubitril/Valsartan), Entresto™ Summary and Practical Tips

Mechanism of action: sacubitril is a neprilysin (endopeptidase) inhibitor: ↑vasodilatory peptides → ↑sodium loss, ↓hypertrophy/remodeling. Combination with an ARB is necessary as inhibition of neprilysin leads to activation of the renin angiotensin aldosterone system (RAAS).

Indication:

- Health Canada Indication[1]: heart failure with reduced ejection fraction (HFrEF), NYHA class II-III, in combination with other heart failure (HF) therapies in place of an ACEI or ARB
- CCS HF 2014 Guidelines[2]: mild-moderate HF, left ventricular ejection fraction (LVEF) <40%, ↑ natriuretic peptides or hospitalization for HF in past 12 months, K+ <5.2, eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy

PARADIGM inclusion[3]	PARADIGM exclusion[3]
• NYHA class II-IV • LVEF ≤ 40% • BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) OR hospitalization for HF in the past year and BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) • Stable dose of ACEI or ARB (equivalent to enalapril ≥ 10 mg/d) and β-blocker for ≥ 4 weeks	• Hypotension (symptomatic, systolic blood pressure [SBP] < 100 mmHg) • eGFR <30 mL/min • K > 5.2 mmol/L • History of angioedema

Dosing:

- Tablet: film-coated, unscored containing both sacubitril and valsartan (dose is sum of agents)
- Strengths**: 50 mg** (24/26mg; white), **100 mg** (49/51mg; yellow), **200 mg** (97/103mg; pink)
  - Note: different valsartan salts; Entresto™ valsartan 103mg = Diovan™ valsartan 160 mg
- Target dose: 200 mg PO BID[1,3]
  - mean dose in PARADIGM= 375mg/d, 76% on target dose[3]

Converting to LCZ696:[1]

- FROM ACEI: Stop ACEI, **wait at least 36 h** after last dose (↑ risk of angioedema), then start
- FROM ARB: Stop ARB, no washout period necessary, start when next dose would have been due

Initial dose and titration:[1,3,4]

High dose RAAS inhibitor		**Initial Dose**	**Titration**
ACEI	ARB		
Enalapril ≥10mg/d lisinopril ≥10 mg/d perindopril ≥4 mg/d ramipril ≥5 mg/d	candesartan ≥16mg/d irbesartan ≥150 mg/d losartan ≥50 mg/d olmesartan ≥10 mg/d telmisartan ≥40 mg/d valsartan ≥160 mg/d	**100 mg PO BID**[3]	Increase in **3-6 weeks** to target 200 mg PO BID[3,4]
Low dose RAAS inhibitor		***50 - 100mg PO BID**[1,4]	**Over 6 weeks**, increase to target 200 mg PO BID[4]
RAAS naïve		***50mg PO BID**[1,4]	
Higher risk of hypotension (eg. low baseline SBP)			

* Note: little data available using the 50 mg BID dose. PARADIGM had an option to down-titrate to 50mg BID, but no data was reported on the frequency of use.[3] TITRATION used 50mg BID as the starting dose for all patients (n=429). Few were RAAS naïve n = 30.[4]

Monitoring:

- Same as RAAS inhibitors.
- Angioedema: stop LCZ696, contact physician, do not re-challenge.
- Note: LCZ696 is expected to raise BNP levels, but not NT-proBNP[1]

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PARADIGM Efficacy/Safety Summary[3]

Endpoints	LCZ696 200 mg BID (n=4187)	Enalapril 10 mg BID (n=4212)	HR (95% CI)
Primary Endpoint			
Composite CV death & 1st hospitalization for worsening HF	**21.8%**	26.5%	0.80 (0.73-0.87)
Secondary Endpoints			
CV death	**13.3%**	16.5%	0.80 (0.71-0.89)
1st hospitalization for worsening HF	**12.8%**	15.6%	0.79 (0.71-0.89)
Death from any cause	**17%**	19.8%	0.84 (0.76-0.93)
Decline in renal function (ESRD, ↑≥50%, ↓30 - 60 mL/min)	2.2%	2.6%	0.86 (0.65-1.13)
Safety Endpoints			
Symptomatic hypotension	**14%**	9.2%	
Symptomatic hypotension & SBP <90 mmHg	**2.7%**	1.4%	
Scr ≥221 µmol/L	3.3%	**4.5%**	
K+ >5.5 mmol/L	16.1%	17.3%	NS
K+ >6.0 mmol/L	4.3%	**5.6%**	
Cough	11.3%	**14.3%**	
Angioedema	0.45%	0.24%	NS
Permanent study drug discontinuation			
Hypotension	0.9%	0.7%	NS
Renal impairment	0.7%	**1.4%**	
Hyperkalemia	0.3%	0.4%	NS

NS = not statistically significant

Pharmacokinetics[1]

- Sacubitril is a prodrug metabolized via esterases to LBQ657 (active metabolite); inhibits OATP1B1 and OAT1B3; 52-68% of LBQ657 is excreted in the urine
- Increase exposure in elderly subjects by 42%/30% (LBQ657/valsartan)
- Increase exposure of LBQ657 in renal dysfunction; 2.7 fold higher in those with eGFR<30ml/min/1.73m
- Food has no impact on systemic exposure
- Half-life: LBQ657 (active metabolite of sacubitril) = 11.5 h and valsartan= 10 h
- Drug interactions
    - Same as per valsartan / ARBs
    - Atorvastatin – increase Cmax 2 fold and AUC 1.3 fold of atorvastatin
    - Simvastatin – may increase levels of simvastatin
    - Sildenafil – additional BP lowering effect (5/4mmHg)

References

1. ENTRESTO (sacubitril/valsartan) Product Monograph. Novartis Pharmaceuticals Canada Inc. October 2, 2015.

2. Moe GW, Ezekowitz JAE, O'Meara E, et al. The 2014 CCS Heart Failure Management Guideline Focus Update. Can J Card 2015; 31: 3-16.

3. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371: 993-1004.

4. Senni M, Reyes A, Majercak, I, et al. Results of the TITRATION study: A 12-week, multicentre, randomized, double-blind, safety evaluation of a 3- versus 6-week up-titration regimen of LCZ696 in patients with HFrEF. Eur J Heart Fail 2015. Conference: Heart Failure 2015 and the 2nd World Congress on Acute Heart Failure. Seville, Spain. Conference Publication: 17 (pp 393), 2015. Date of Publication: May 2015.

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