Entresto
(sacubitril / valsartn)

Contents

01

Place in therapy

Heart Failure

Entresto (sacubitril / valsartn)

"Used mainly in Heart Failure ".

Place in therapy:

- Patients with chronic symptomatic class II-III **HFrEF**
- In replacement to current **ACEI/ARB**
- In addition to beta-blockers
- **Reduced morbidity/mortality. (BG therapy)**

- **In a recent case series, four patients with chemotherapy-related acute cardiac failure with severely reduced ejection fraction were successfully treated with sacubitril/valsartan.**
- **Sacubitril/valsartan was also demonstrated to be valuable in anthracycline-related cardiac toxicity**
- **In a recent clinical trial, sacubitril/valsartan emerged as a promising treatment option in patients with refractory CTRCD.**

02

Pharmacological category

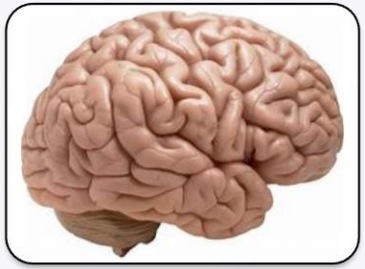
Angiotensin receptor-Neprilysin inhibitor (ARNI)

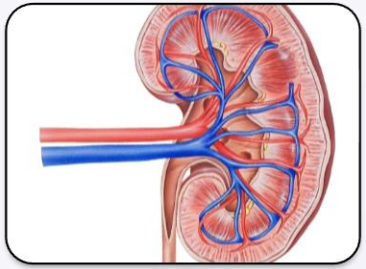
03

Mechanism of action

How ARNI works ?

Heart Failure and Compensatory Mechanisms





NPS ↑

1- Elevated BNP and NT-pro BNP

2- Naturitic diuresis (BV)

3- Dec BP ↓

BR

1- SNS activation

2- HR ↑

3- BP ↑

3- CO ↑

RAAS

1- Renin sec ↑

2- Na/H2o retention

3- BP ↑

4- Co ↑

Cardiac Remolding

1- Ventricular wall distention

2- Myocyte growth

3- Hypertrophy

NPS : **decreases blood pressure (BP) , lowers the sympathetic tone**, **and** **reduces aldosterone levels**. **antagonistically to the RAAS** and has **favorable effects on the pathogenesis of heart failure**

Sacubitril/valsartan is a combination product. Where it's a pro-drug that, upon activation, acts as ARNI :

Sacubitril

(Nypralisin inhibitor)

- **Block the action of neprilysin,**
- **Thus preventing the breakdown of natriuretic peptides,**
- **Prolonged duration of the favorable effects of these peptides**

Valsartan

(ARBS)

- Blocking the RAAS system.
- Dec BP and CO

However, because **neprilysin breaks down angiotensin II & Bradykinin**,
So inhibiting neprilysin will **accumulate Ang. II. & Bradykinin**

For this reason, a **neprilysin inhibitor cannot be used alone**; it must always be combined with an ARB **to block the effect of the excess angiotensin II**

Monitoring Parameter

- ✓ **NOTE for Monitoring Parameter :**
- ✓ **Because sacubitril/valsartan therapy inhibits the breakdown of brain natriuretic peptide (BNP) :**

Therefore :

- ➢ **BNP will be elevated in patients taking this drug.** **BNP will not be a reliable marker of heart failure exacerbations** in these patients.
- ➢ NT-pro-BNP is not a substrate for neprilysin and is therefore not affected by sacubitril. Therefore, **NT-pro-BNP should be utilized** in patients on sacubitril/valsartan when **a heart failure exacerbation is suspected**

04

Administration

Entresto Admisntration ?

- Sacubitril/valsartan is available as an **oral tablet in three dosage strengths containing :**

✓ **Sacubitril** (24 mg, 49 mg, or 97 mg)
✓ **Valsartan** (26 mg, 51 mg, or 103 mg).

- Valsartan component in this combination has a **higher bioavailability** than regular valsartan tablets :

➢ **Valsartan 26 mg**, **51 mg**, and **103 mg** in the brand-name combination are **equivalent to valsartan 40 mg**, **80 mg**, and **160 mg** in other formulations, respectively

.

Entresto Admisntration ?

- **Twice a day (BID)** and maybe administered without regard to meals.
- Allow at least a **36-hour washout period** when switching from an **ACEI** before starting sacubitril/valsartan.
- Patients **must be tolerated an ACEI or an ARB** before being started on sacubitril/valsartan.
- Clinicians can replace sacubitril/valsartan **oral suspension** at the recommended tablet dosage in patients unable to swallow tablets.

05

Pediatric dose

Pediatric dose :

Table 1: Recommended Dose Titration

	Titration Step Dose (twice daily)		
	Starting	Second	Final
Pediatric Patients Less than 40 kg†	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Patients At least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg‡
Pediatric Patients At least 50 kg	49/51 mg	72/78 mg‡	97/103 mg

- Mild to moderate Kidney impairment (eGFR ≥30 mL/minute/1.73 m^2):

No dosage adjustment necessary.

- **Severe impairment** (eGFR <30 mL/minute/1.73 m^2):

Initial:

Reduce the usual starting dose by 50%, then follow the recommended dose escalation to titrate dose.

06 Toxcicity

Adverse Effects

- **Hypotension,**
- **Hyperkalemia,**
- **Renal failure,**
- **Cough**,

➢ **Note** :

Sacubitril/valsartan was associated with :

✓lower risk of elevation in **serum potassium** or serum creatinine and a lower risk of cough than enalapril.

✓More patients experienced **angioedema** in the sacubitril/valsartan arm than in the enalapril; however, this outcome was not statistically significant

Contraindications

❑ **Hypersensitivity**

❑**History of angioedema** due to an ACEI or ARBs

❑ In **diabetic patients** receiving the renin inhibitor, **aliskiren,** specifically, the valsartan (any ARB), is contraindicated with aliskiren due to an **increased risk of hypotension, hyperkalemia, and renal impairment**.

❑Patients who have received an **ACE-inhibitors within 36 hours** due to increased risk of angioedema,

Box warning

❖Drugs that work directly on the renin-angiotensin system, injury and/or death to the developing fetus. When pregnancy is confirmed, discontinue sacubitril/valsartan as soon as possible

Toxicity of Entresto

Limited literature is available concerning toxicity in human subjects. However, a **single dose** of **583 mg sacubitril/617 mg valsartan i**n healthy volunteers and **multiple doses of 437 mg sacubitril and 463 mg valsartan** for **14 days** were studied. **Hypotension resulting from overdose requires prompt treatment**.

- In pharmacokinetics, sacubitril is converted to **LBQ657** (active metabolized compound)
- All three compounds (sacubitril, LBQ657, and valsartan) are **highly bound (94% to 97%) to plasma protein**.
- Hence, it is **unlikely to be removed by hemodialysis.**

07

Drug Interactions

Drug interactions

1- Aliskiren:

- ❑ May enhance the **hyperkalemic effect** of Angiotensin II Receptor Blockers.
- ❑ May enhance the **hypotensive effect** of Angiotensin II Receptor Blockers.
- ❑ May enhance the **nephrotoxic effect** of Angiotensin II Receptor Blockers.
- ➢ **Management:** Aliskiren use with ACEIs or ARBs in patients with diabetes is contraindicated

❖ ***Risk D: Consider therapy modification***

2- Amifostine:

- ❑ Blood Pressure Lowering Agents may enhance the hypotensive effect of Amifostine.

- ➢ **Management:** When used at chemotherapy doses, hold blood pressure lowering medications for 24 hours before amifostine administration.

❖ ***Risk D: Consider therapy modification***

3- Angiotensin-Converting Enzyme Inhibitors: (ACEI)

- ❑ May enhance the **adverse/toxic effect of Sacubitril**. (bradykinin ↑)
- ❑ Specifically, the risk of **angioedema** may be increased with this combination.

❖ ***Risk X: Avoid combination***

08

Patient Education

Patient Education

- ✓ Entresto is usually given **twice daily**.
- ✓ May be taken with or without food.
- ✓ Report any signs or symptoms of **angioedema** :
  (swelling of the face or throat, difficulty breathing)
  immediately to your doctor.
- ✓ May cause a fall in blood pressure that may be noticed as **light-headedness**; call your doctor and ask for advice, symptoms usually resolve with continued therapy.
- ✓ Ensure you **do not become dehydrated**.

Patient Education

- ✓ **Do not use salt substitutes containing potassium without first consulting your doctor.**
- ✓ **Entresto is usually used in addition to other drugs to lower blood pressure, and all lifestyle recommendations given to you by your doctor (such as losing weight if overweight, smoking cessation, partaking in regular exercise, and imitinlg sodium intake) should also be followed.**
- ✓ **In addition, other conditions, such as high cholesterol levels or diabetes if present, also need to be controlled.**
- ✓ **Do not take any other medications including those bought over-the-counter without checking with your doctor or pharmacist.**

Thanks

Do you have any questions?

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