The Newcastle upon Tyne Hospitals NHS Foundation Trust

Sacubitril with Valsartan (Entresto ®) use for heart failure in paediatric patients within cardiothoracic services

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1 Introduction

Entresto® is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB). This benefits heart failure patients with dual action effect.

Sacubitril is a pro-drug that metabolises to LBQ657 which directly inhibits neprilysin, a neutral endopeptidase. Neprilysin cleaves natriuretic peptides, however with its inhibition, this leads to reduced breakdown thus increased concentration of endogenous natriuretic peptides. This leads to enhanced natriuretic, diuretic and vasodilator actions [1][2].

Valsartan inhibits angiotensin II by selectively blocking angiotensin I receptors and inhibiting angiotensin II- dependant aldosterone release, thus inhibiting detrimental cardiovascular and renal effects of angiotensin II [1].

Entresto has been used widely in the treatment of adult heart failure. The PANARMA-HF has shown **no** significant differences were observed in the global rank primary end point between Sacubitril/Valsartan and Enalapril treatment in pediatric patients with HF with systemic LVSD. There was evidence of a possible health-related quality-of-life advantage of Sacubitril/Valsartan over Enalapril [2].

2 Guideline scope

This guideline is aimed for the use of Entresto in paediatric patients between 1 – 18 years old, for the treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction. This guideline is to be used trust wide within the paediatric cardiothoracic patient cohort.

This guideline provides guidance on the prescribing, administration and monitoring of initiation and maintenance doses of Entresto.

Entresto should be considered if patients are symptomatic despite optimal medical therapy including ACE-Inhibitor or angiotensin receptor antagonist. They should also be on beta-blocker (unless contra-indicated). Given the degree of hypotension associated with Entresto, it would be advisable to not to commence Entresto until patients are stabilised on oral therapy and off inotropes. (3)

Blueteqs must be completed for patients being prescribed Entresto.

3 Guideline

3.1 Initiation of Entresto

Prior to starting Entresto, if patient is currently taking an ACEi (Enalapril, Captopril)/ARB (losartan), this should be **discontinued for at least 36 hours** prior to initiation of Entresto. This is to minimise risk of angioedema due to dual blockade of renin-angiotensin-aldosterone system [1][2].

There are no contraindications for starting Entresto alongside heart failure medications EXCEPT ACEi's and ARBs as detailed above.

Do not initiate Entresto in patients <5th centile BP and/or serum K+ >5.3.

Please note that all dosing are the combined strength of both Sacubitril and Valsartan.

3.2 Entresto dosing information

Patient weight	Give TWICE a day	
	Test dose/half dose (Day 0)*	Starting dose (Day 1) if no adverse reaction from initiation
<40kg	0.8mg/kg	1.6mg/kg (up to a maximum of 24/26mg)
>40kg - <50kg	0.8mg/kg	24mg/26mg
>50kg	24mg/26mg	49mg/51mg

- * Test dose/half starting dose recommended in patients:
  - taking low doses or have previously not tolerated ACE inhibitor or an angiotensin receptor blocker
  - who have renal impairment (eGFR <60 ml/min/1.73 m^2)
  - who have moderate hepatic impairment or if hepatic transaminases exceed 2 times the upper limit of normal,

If observations allow, Entresto dose can be optimised further.

Patient weight	Give TWICE a day		
	Half/test dose*	Starting dose	Up to a Maximum dose
<40kg	0.8mg/kg	1.6mg/kg (up to a maximum 24/26mg)	3.1mg/kg
>40kg - <50kg	0.8mg/kg	24mg/26mg	72mg/78mg
>50kg	24mg/26mg	49mg/51mg	97mg/103mg

In the current patient cohort, side effects of Entresto (primarily hypotension) meant that we have struggled to increase past maintenance dosing.

Entresto can be up titrated slowly (by 0.2mg/kg every 2 weeks) to reach optimal doses or speak to heart failure cardiologist.

3.2.1 Renal impairment:

- Entresto is cautioned in renal impairment – due to increased risk of hypotension. There is limited information available in severe impairment

- Avoid in end stage renal disease (no information available)

3.2.2 Hepatic impairment:

- Avoid in severe impairment, biliary cirrhosis or cholestatis (no information available)

- Caution in moderate impairment or ALT/AST that exceed 2 times upper limit of normal.

3.3 Administration of Entresto

Entresto is only available for oral administration.

There is no information regarding administration of Entresto via enteral feeding tubes, however granules should not be used as likely to clog up enteral feeding tubes. Formulations available in pharmacy:

- Valsartan 6mg / Sacubitril 6mg granules (in capsules for opening)
- Valsartan 16mg / Sacubitril 15mg granules (in capsules for opening)
- Valsartan 26mg / Sacubitril 24mg tablets
- Valsartan 51mg / Sacubitril 49mg tablets

- Valsartan 103mg / Sacubitril 97mg tablets

0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using granules in capsules for opening. Doses should be rounded to the nearest full capsule. Weight based dosing should be given using granules (licensed formulation) however tablets can be considered as an off label use if appropriate.

For example, a paediatric patient weighing 25 kg who has not previously taken an ACE inhibitor should start with half the standard starting dose, which corresponds to 20 mg (25 kg × 0.8 mg/kg) twice daily, given as granules. After rounding to the closest number of full capsules, this corresponds to 2 capsules of 6 mg/6 mg sacubitril/valsartan twice daily.

The approved administration for Entresto granules is to open capsule, sprinkle over soft food (1-2 teaspoons) and ingest immediately. Capsules should not be swallowed whole. The empty shells must be discarded after use and not swallowed.

If tablet administration For doses <50mg (combined total of valsartan and sacubitril, equivalent to 26mg / 24mg tablet), crush and disperse tablets in 10mL of water and give a proportion. For example, if a patient is prescribed 25mg BD, crush and disperse 1 x 26mg/24mg tablet in 10mL of water and give 5mL.

3.4 Monitoring requirements for Inpatients

Blood pressure

Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with Sacubitril/Valsartan, however, such corrective action must be carefully weighed against the risk of volume overload.

Patients who are at risk of hypotension may need blood pressure monitored routinely during dose initiation and titration. All patients should be warned of first dose hypotension and therapy should not be initiated if systolic blood pressure is <5th percentile for the age of the patient.

Renal function

Prior to initiation, U+Es should be taken to assess baseline renal function and potassium. This should be repeated 24 hours after initiating Entresto, 24 hours after every dose change and prior to discharge. Entresto should be withheld if renal function declines. Re-test after withholding and restart Entresto at a lower dose if renal function improves.

FBCs and LFTs should also be checked

BNP is not a suitable biomarker of heart failure in patients treated with Sacubitril/Valsartan because it is a neprilysin substrate

3.5 Contraindications:

- Hypersensitivity to the active substances or to any of the excipients of product.
- Concomitant use with ACE inhibitors. Entresto must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy Hereditary or idiopathic angioedema
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2)
- Severe hepatic impairment, biliary cirrhosis and cholestasis

3.6 Cautions:

- Renal artery stenosis
- Renal impairment
- NHYA functional Class 4
- Hepatic impairment

3.7 Interactions:

Agent	Type of interaction	Recommendation
ACE inhibitors	Concomitant use is contraindicated may increase risk of angioedema (1)	Sacubitril/valsartan must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (1)
ARB therapy	Sacubitril/valsartan contains valsartan, and therefore should not be co-administered with another ARB containing medicinal produc	
Drugs which may increase potassium including spironolactone,	Concomitant use may lead to increase in serum potassium and to increase serum creatinine (1)	Monitoring of serum potassium is recommended if Entresto is co-administered.

potassium supplements		
Statins	Entresto inhibits metabolising enzyme of statins. Therefore, exposure to statins is increased [1]	Monitor for statin adverse effects. Reduce statin dose or discontinue statin if these occur.
NSAIDS/ COX-2 inhibitors	May increase risk of reduced renal function with concomitant use [1]	Use paracetamol initially for pain relief. If ibuprofen is required, monitor renal function. Use alternative pain relief if renal function deteriorates.
Ciclosporin	Ciclosporin may inhibit the metabolising enzyme of Entresto. Therefore, exposure to Entresto is increased [1]	Monitor BP, adjust Entresto dose where necessary.

3.8 – Adverse Events:

- Hyperkalaemia/hypokalaemia/hypoglycaemia/hyponatraemia.
- Anaemia
- Hypotension
- Renal impairment/Renal failure
- GI side effects (nausea, diarrhoea, gastritis)
- Dizziness, Headache, Syncope, vertigo
- Cough
- Fatigue/Asthenia
- For further information see BNFc

Appendices

4 Monitoring Section (TBC)

The organisation continually strives to achieve 100% compliance with this guideline and its intended outcomes. Where this is not met an action plan will be formulated and reviewed until completion. Please see the table below for standards and monitoring arrangements:

Standards	***Monitoring and audit***			
	Method	***By***	***Group / Committee***	***Frequency***
This should be the steps that you have described in the process part of the guideline for example: *All inpatients will receive an initial EWS score within an hour of admission*	This is how are you going to monitor this, for example: Snapshot random audit Quality assurance audit	Who will undertake the monitoring: *Infant feeding lead*	Who has overall accountability: *CGQ*	How often are these carried out: at least monthly quarterly
Once you have pulled all the standards out of the guideline you then need to put in your outcome standards, for example: *Reduction in the rate of unexpected cardiac arrests*	Outcomes may be monitored differently for example: Review of all incidents of unexpected cardiac arrests Review of rates and reasons of cardiac arrests	As above	As above	If this is a review of incidents or complaints etc it should be continuous Continuously Annually

The audit tool should be included as an appendix to the guideline.

5 Evidence Review and Evaluation (TBC)

Author of the Guidelines	Catriona Johnston/Katherine Stutz (specialist paediatric pharmacist) Abbas Khushnood (Paediatric Cardiology consultant)
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6 References

1. Entresto 24 mg/26 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

2. Baseline Characteristics of Pediatric Patients With Heart Failure Due to Systemic Left Ventricular Systolic Dysfunction in the PANORAMA-HF Trial | Circulation: Heart Failure (ahajournals.org)

3. Great Ormond Street Guideline, **Sacubitril with Valsartan for Heart Failure**

4. BNFc - MedicinesComplete — CONTENT > BNF for Children > Drug: Sacubitril with valsartan

5. **GSTT clinibee monograph**