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Treatment of Moderate or Severe Left Ventricular Systolic Dysfunction in Primary Care and Outpatient Setting

GENERAL

- If possible, discontinue aggravating drugs e.g. NSAID, verapamil, diltiazem and thiazolidinediones
- Address non-pharmacological + self-care measures e.g. smoking, alcohol + fluid intake, diet (salt intake), exercise, obesity
- Advise about treatment adherence and seeking early advice regarding symptom deterioration
- Annual influenza and once-only pneumococcal immunisation
- Patient-held record of treatment, weight, risk factors etc.
- Primary/secondary prevention of coronary artery disease and hypertension
- Refer to Cardiac Rehabilitation – if available in local area

TREATMENT

A - Assess for signs of water retention e.g. oedema, lung crackles, raised JVP or congestion on CXR

- Start oral loop diuretic (furosemide or bumetanide) and stop existing thiazides e.g. bendroflumethiazide
- If already on loop diuretics, increase dose or switch furosemide to bumetanide if signs of water retention

B – Treatment for moderate or severe LVSD

- Start ACE inhibitor (ACEi)* or ARB if not tolerated **and** a beta blocker* (BB) and up titrate to maximum tolerated doses
- Commence mineralocorticoid receptor antagonist (MRA) if severe LVSD e.g. spironolactone* or eplerenone*

C - Ongoing symptoms

- Ensure on maximum tolerated dose of ACEi/Angiotensin Receptor Blocker (ARB) and beta blocker (BB)
- Consider adding a mineralocorticoid receptor antagonist (MRA) in mod-severe LVSD e.g. spironolactone* or Eplerenone*
- Consider switching ACEi/ARB to sacubitril/valsartan* if severe LVSD in NYHA II-IV - refer for specialist initiation
- Consider referral to specialist to initiate dapagliflozin *. Can be started on the advice of a HF specialist as an add-on to optimised standard care with or without Type 2 Diabetes Mellitus (T2DM)
- Consider adding Ivabradine* if severe LVSD **and** resting HR≥75 with sinus rhythm (do not use in any supraventricular tachycardia e.g. AF, A flutter)
- Consider referral for CRT +/- ICD if QRS ≥130 and severe LVSD - discuss with HF MDT / Cardiologist
- Consider adding low dose digoxin (even in SR)). Aim for lower levels of 0.7-1.0mcg/L in patients without AF (do not use in combination with ivabradine)

ICD'S with mod-severe LVSD

- Consider an ICD for primary prevention in NYHA II-III, EF<35% despite 3/12 optimal medical therapy and >1 year expected survival in patients with dilated cardiomyopathy and IHD (>40 days post MI)
- Consider an ICD for secondary prevention for patients recovered from haemodynamically unstable ventricular arrhythmia and >1 years expected survival

ASSOCIATED PROBLEMS

Hypotension

- Stop/reduce non-HF medication first if possible
- If dehydrated clinically and/or biochemically, reduce diuretics
- If bradycardic on a BB, reduce dose - no sudden stopping if possible (risk of rebound tachycardia)
- If persistent and symptomatic, refer to HF team

Atrial fibrillation

- If ventricular-rate (VR) >90bpm increase beta-blocker or add oral digoxin if BP low
- If rate >110bpm despite maximum tolerated oral treatment, refer for consideration of amiodarone +/- DCCV +/- ablation
- If new onset AF ≥24 hours with fast VR, refer to hospital
- Consider anti-coagulation (unless contra-indicated) – see AF Thromboprophylaxis pathway

Unresponsive to medical treatment

- Consider day-case/community SC/IV diuretics (via Cardiac Ambulatory unit/Hospice) – applicable to West Cheshire only
- In diuretic-resistant patients consider adding bendroflumethiazide /metolazone (2nd line) with loop diuretics (under HF team review)
- Discuss with Cardiologist if heart transplantation/bridging therapy could be considered
- If persistent hyperkalaemia (>6) refer to secondary care for advice
- For palliative patients consider referral to the local Hospice and Palliative Care services

Angina

- Consider up-titration of beta-blocker
- Consider oral nitrates and/or amlodipine
- Consider ivabradine
- Consider referral to Cardiologist if new onset or unresponsive to treatment

* See appropriate algorithm

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Algorithm for the use of an Ace Inhibitor in Heart Failure

Confirmed Left Ventricular Systolic Dysfunction
(Mod-severe LVSD on echocardiography)

↓

Suitable for initiation of ACE inhibitor (ACEi)?

↓

Specialist Medical advice required before starting ACE-I in the following groups

- Creatinine eGFR <30mls/min
- Sodium <130 mmol/l
- Systolic arterial pressure <100mm Hg
- Diuretic dose > Furosemide 120 mg/day or equivalent

Contraindications:

- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Pregnancy
- History of angioedema

Caution in moderate-severe aortic stenosis.

Initiation of ACE inhibitor

- Stop potassium supplements/potassium sparing diuretics apart from Spironolactone or Eplerenone
- Stop NSAID (because of risk of renal dysfunction + HF)
- Before starting ACEi, educate patient about purpose, benefits and possible side effects
- Start low dose ACEi Ramipril 1.25mg daily if on concurrent diuretics, frail, elderly, hypotensive or CrCl <30mls/min (Ramipril recommended as first choice as per formulary) otherwise could initiate at 2.5mg daily
- Check U&E prior to initiation, at 1 and 4 weeks, and following each titration step. Monitor BP
- Monitor for adverse effects (see below)
- Titrate at 1-2 weekly intervals to target dose or maximum tolerated dose (see table 1).

On maximal tolerated dose

- Check U&E 6 monthly and continue to monitor for adverse effects

Potential adverse effects of ACE inhibitors

- symptomatic hypotension, renal dysfunction (accept if <50% rise in creatinine to eGFR <30mls/min), hyperkalaemia (rise in K+to >5.5mmol/l), intolerable cough (NOT just dry cough)

Table 1 Ramipril dose schedules

Start at 1.25mg once daily
Increase gradually at intervals of 1-2 weeks
Only titrate following U/E check after each dose increment

Daily dose
1.25mg daily
2.5mg daily or 1.25mg twice a day
5mg daily or 2.5mg twice a day
10mg daily or 5mg twice a day

- Smaller incremental increases can be considered in frail, elderly, hypotensive or renal patients
- CrCl/eGFR 10-60mls/min = max dose 5mg/day
- If using alternative ACEi, refer to BNF or SPC

If truly intolerant of ACE inhibitor consider angiotensin II receptor antagonist

- Candesartan is the ARB of choice
- Consider Candesartan 4mg daily up-titrated to 32mg daily or maximum tolerated dose.
- Up-titration similar to ACE inhibitor protocol
- Candesartan titration steps (4mg daily, 8mg daily, 16mg daily and 32mg daily)

If intolerant of ACE inhibitor, Angiotensin-II Receptor antagonists and sacubitril valsartan:

- Consider Hydralazine 25mg twice a day and Isosorbide mononitrate (ISMN) MR 30mg daily as an alternative. Increase as tolerated to 25mg three times a day up to a maximum daily dose of hydralazine 300mg (split over three or four times a day dosing) and ISMN MR 120mg daily (seek specialist advice) according to response.

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Algorithm for the use of a **Beta-blocker** in Heart Failure

Confirmed Left Ventricular Systolic Dysfunction
(Mod-severe LVSD on echocardiography)

↓

Suitable for initiation of Beta-blocker?

↓

Beta-Blocker contraindicated in:

- Asthma (bisoprolol and nebivolol can be tried)
- 2nd /3rd degree AV Heart Block/sick sinus syndrome
- See SPC for full details

Beta-blockers can still be used with caution in the following (NICE 2010):

- Elderly
- Chronic obstructive pulmonary disease without reversibility
- Peripheral vascular disease
- Diabetes mellitus
- Interstitial pulmonary disease
- Erectile dysfunction

1st Line Beta-blocker

Bisoprolol Dose Schedule

1.25mg daily >1 week: if tolerated increase
2.5mg daily >1 week: if tolerated increase
3.75mg daily >1 week: if tolerated increase
5mg daily >4 week: if tolerated increase
7.5mg daily >4 week: if tolerated increase
10mg daily Maintenance dose

If any concerns with low heart rate consider using Carvedilol:

Carvedilol Dose Schedule

3.125mg twice a day >2 weeks:if tolerated increase
6.25mg twice a day >2 weeks: if tolerated increase
12.5mg twice a day >2 weeks: if tolerated increase
25mg twice a day Maintenance dose
If Weight >85kg and tolerating 25mg twice a day, consider increasing to 50mg twice a day > 2 weeks

Nebivolol can be considered if bisoprolol or carvedilol are not tolerated e.g. wheeze/bronchospasm.

Nebivolol Dose Schedule

1.25mg daily >1 week: if tolerated increase
2.5mg daily >1 week: if tolerated increase
5mg daily >4 week: if tolerated increase
10mg daily Maintenance dose

Initiation of Beta Blocker

- Clinically stable heart failure (NYHA I-III)
- No signs of water retention (oedema, lung crackles, raised JVP or congestion on CXR)
- Heart Rate >60bpm & no heart block on recent ECG
- In AF, ventricular rates of <70 bpm are associated with worse outcomes (unless required for NSVT, ectopics etc.)
- Systolic blood pressure>100mmHg or asymptomatic hypotension >90mmHg
- No Contraindications
- Start with lowest recommended dose (dose can be split twice daily as up-titrated)
- Educate patients re: purpose, benefits and signs of worsening heart failure, not to stop abruptly without advice
- If taking other rate reducing medication, consider reduction in dose
- Do not use a combination of more than two rate limiting medications

Monitoring

- **Up titration of dose as per dosing schedule**
- **Check for adverse side-effects**
  - **Worsening heart failure** - Consider adding or increasing dose of loop diuretic.
  - **Symptomatic hypotension** – consider reduction of diuretic if no congestion. Consider reduction of other vasodilators e.g. calcium channel blockers, nitrates
  - **Excessive bradycardia (<50 bpm)** –If taking other rate sparing medication, consider reduction in dose. Consider halving beta-blocker
  - **Marked fatigue** – reassure patient of likely improvement in symptoms. Review in 2 weeks

↓

If intolerant of Beta-Blocker

- Consider reducing dose and review in 2 weeks.
- Consider stopping and/or seek specialist advice

Beta- blockers should not be stopped suddenly unless absolutely necessary - Aim to reduce dose or tail off slowly to zero if patient develops problems

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Algorithm for the use of Mineralocorticoid Receptor Antagonist (MRA) in Heart Failure

Confirmed Left Ventricular Systolic Dysfunction

Consider for all LVSD patients who remain symptomatic despite treatment with an ACE inhibitor and a beta blocker.

↓

Suitable for initiation of Mineralocorticoid receptor antagonist (MRA) (1st line – Spironolactone)

↓

Aldosterone antagonists contraindicated

- Serum potassium > 5mmol/l
- Serum creatinine >eGFR <30mls/min but may be considered
- Caution if mild to moderate renal impairment
- Severe hepatic insufficiency

***Adverse Effects**

Potassium 5.5 – 6.0 mmol/l

- Reduce to 12.5mg daily/ OR consider 25mg alternate days administration
- Repeat bloods 5-7 days later

Potassium >6.0 mmol/l

- STOP aldosterone antagonist
- Repeat bloods 5-7 days later and consider re-introduction at 12.5mg daily or 25mgon alternate days

Intolerant to spironolactone

- Consider reducing dose to 12.5mg daily or 25mg on alternate days. If necessary, stop.

Gastro-Intestinal Disturbance

- **Diarrhoea – Stop aldosterone antagonist** and repeat U&E's at earliest convenience

↓

Serum potassium (mmol/L)	Action	Dose adjustment
< 5.0	Increase	25mg every other day to 25mg daily 25mg daily to 50mg daily
5.0 – 5.4	Maintain	No dose adjustment
5.5 – 5.9	Decrease	50mg daily to 25mg daily 25mg daily to 25mg every other day 25mg every other day to withhold
≥ 6.0	Withhold	N/A

Eplerenone

- Indicated 3-14 days post-MI with EF≤40% NYHA I-II
- Chronic heart failure NYHA Class II **and** severe LVSD
- Intolerable Gynaecomastia on spironolactone
- Aim to titrate dose up to 50mg daily as tolerated
- Monitor K+ as per table above
- Eplerenone cannot be dosed at 12.5mg, give 25mg every other day

Step 1
Assess whether suitable for treatment

- Current or previous NYHA II-IV symptomatic heart failure
- Already on ACE inhibitor and beta blockers (unless contraindicated) +/- diuretic
- No evidence of hypovolaemia

↓

Step 2
Check urea & electrolytes, and review use of potassium supplements and potassium-sparing diuretics

- Potassium must be <5 mmol/l to continue
- Consider stopping potassium supplements and potassium sparing diuretics
- Continue ACE inhibitor, ß-blocker, loop diuretics and digoxin if also prescribed

↓

Step 3
Spironolactone initiation

- Commence at 25mg daily
- Increase to 50mg daily if persistent symptoms and no problems, e.g. hyperkalaemia

↓

Step 4
Monitoring

- Check U+E at weeks 1 & 4 after initiation and at each dose change
- Thereafter U+E should be checked monthly (8 & 12 weeks) until 3 months then at least 6 monthly
- Unstable patients (renal dysfunction, history of previous high K+) should have U+E checked 3 monthly
- U+ES should be rechecked if patients become unwell

Inform patient of purpose, benefits & possible side effects of MRA's.

Heart Failure Guidelines Appendix C – Aldosterone antagonists
Cheshire Version 1.0 based on CoCH Version written by Dr John Somauroo, Dr Benopoulos, Diana Astbury HFSN (Community) and Jo Bateman, HF specialist Pharmacist
Approved at APG on 18 March 2021 Review date: March 2023

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Algorithm for the use of Ivabradine in Heart Failure

Inadequate Heart Rate Control ≥75bpm for patients in sinus rhythm

- **Maximise beta blocker dose before considering ivabradine**

Initiate as per NICE TA 267:

- If severe LVSD **and** resting HR≥75 **and** NYHA II-IV
- Should only be initiated after a stabilisation period of 4 weeks on optimised therapy with beta blocker, ACE-I and aldosterone antagonists
- Do NOT start ivabradine instead of a beta blocker unless beta blocker is contra-indicated
- DO NOT use in atrial arrhythmias (e.g. AF) as there is no effect
- Initiation should be by a heart failure specialist prescriber with access to a multidisciplinary team.

Ivabradine is contraindicated in:

- Resting HR <60bpm prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (<90/50mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (HR imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination of strong cytochrome P450 3A4 inhibitors e.g. ketoconazole, clarithromycin, erythromycin, see SPC for full details
- Pregnancy, lactation

Cautions

- In NYHA class IV - limited amount of data
- Consider stopping treatment if unexpected deterioration in visual function occurs (phosphenes are usually self-limiting – see below)
- Patients with congenital QT syndrome or combined with drugs that prolong the QT
- Chronic HF patients with intraventricular conduction defects (LBBB, RBBB, ventricular dyssynchrony) – monitor closely
- Use cautiously if eGFR / CrCl <15mls/min
- Do not use more than two rate limiting medications

Interactions

- Diltiazem or verapamil – not recommended
- Grapefruit juice – restrict intake
- CYP3A4 inducers e.g. rifampicin, St John's wort, barbiturates and phenytoin

Common Side Effects

Includes luminous phenomenon (phosphenes), blurred vision, headache and dizziness, bradycardia

Treatment

Usual ivabradine starting dose:

- 5mg twice daily
- Titrate after 2 weeks of treatment to 7.5mg twice daily if resting HR persistently >60 bpm
- If HR is between 50 – 60 bpm – continue 5mg twice daily
- Do not use a combination of more than two rate limiting medications

Elderly patients (≥75 years)

- Start at 2.5mg twice daily
- Titrate after 2 weeks if resting HR persistently >60 bpm to 5mg twice daily (then as per above)
- If HR is between 50 – 60 bpm – continue 2.5mg twice daily

During treatment, if HR decreases persistently <50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated down to the next lower dose. Treatment must be stopped if HR remains <50 bpm or symptoms of bradycardia

Monitoring

- Monitor regularly for occurrence of AF and obtain an ECG if clinically indicated e.g. exacerbated angina palpitations, irregular pulse. If AF occurs, stop treatment
- Dose titration and monitoring should be carried out by a heart failure specialist or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.
- If remains symptomatic on a beta-blocker and ivabradine in sinus rhythm consider switching ivabradine to digoxin (avoid triple therapy)
- Once patients are stable on a maintenance dose, care may be transferred back to the GP

Pathway for the use of SGLT2 inhibitors in Heart Failure with Reduced Ejection Fraction (HFrEF)

Confirmed moderate or severe left ventricular systolic dysfunction on echocardiography (LVEF ≤40%)

Consider dapagliflozin or empagliflozin if symptomatic despite optimal therapy with:

- ACE inhibitor / ARB or sacubitril/valsartan ***and***
- beta blocker ***and***
- mineralocorticoid receptor antagonist (MRAs) if tolerated

Heart Failure specialists may recommend initiating in a different order according to patient tolerability – see stage 3 of the regional HF Pathway **(LINK)**

Consider cautions and contra-indications:

Contraindications

- Allergy to SGLT2 inhibitors
- Type 1 diabetes
- Pregnancy

Should not use if:

- Previous diabetic ketoacidosis (DKA)
- High risk of DKA e.g. previous pancreatitis, starvation – see SPC for full details: Dapagliflozin / Empagliflozin
- Dapagliflozin is licensed for eGFR ≥15ml/ min but limited experience in eGFR <25 ml/min
- Empagliflozin is licensed for eGFR ≥20ml/ min

Cautions

- Previous urosepsis / recurrent genitourinary tracts infections
- Recurrent hypoglycaemia
- Peripheral vascular disease especially if previous amputation or foot ulcer – **discuss with local specialist**
- Raised haematocrit
- Severe liver impairment
- Hypotension (SBP <95 mmHg)
- Elderly patients ≥75 years old may be at increased risk of volume depletion.

Provide Patient Information

Provide manufacturer's patient information leaflet specific for heart failure indication: Dapagliflozin/ Empagliflozin. This may have been supplied by the heart failure team, but it is the responsibility of the prescribing clinician to ensure the patient has received and understands this.

Sick day rules for dapagliflozin / empagliflozin: Stop during acute illness especially if too unwell to eat and drink. Stop 3 days prior to major surgery. Restart when fully recovered and eating and drinking normally.

Diabetic ketoacidosis: For patients with type 2 diabetes mellitus (T2DM), provide education on signs and symptoms of DKA and the need for ketones to be tested even if blood glucose is near normal. Importance of seeking medical help if any signs of DKA or feeling unwell.

Important side effects (not prescriptive – see individual SPCs for dapagliflozin / empagliflozin for full details including frequency):

- Hypoglycaemia when used in combination with insulin or sulfonylureas
- Increased urination and dehydration
- Genital and urinary tract infections
- Allergic reactions including rash / urticaria / angioedema
- Transient rise in creatinine during initial treatment (up to 20%).
- Diabetic ketoacidosis in patient with diabetes - discontinue immediately and DO NOT restart
- Fournier's gangrene (discontinue and initiate treatment promptly)

Pathway for the use of SGLT2 inhibitors in Heart Failure with Reduced Ejection Fraction (HFrEF)

Check baseline bloods: U&Es including eGFR, FBC, LFTs and HbA1c

Assess fluid status and addition of dapagliflozin to diuretic therapy	
Volume status	**Changes to existing therapy**
Euvolaemic patients	Review loop diuretic dose
Volume overload	Add SGLT2 inhibitor to existing diuretics and review diuretic plan
Hypovolaemia	Correct volume depletion before adding SGLT2 inhibitor
Thiazide diuretic for hypertension	Discontinue thiazide and start SGLT2i. GP to review BP in 4-6 weeks. Preference should be to up-titrate ACEi/ARB/ARNI, beta blocker and MRA
Thiazide in combination with a loop diuretic for fluid overload	Discuss with cardiologist
If in doubt, discuss with patient's heart failure specialist	

Type 2 diabetes

No diabetes

Addition of SGLT-2 inhibitors to other glucose lowering medication		
Criteria	**Advice**	**Diabetes Review**
HbA1c <41 (tight control) ***or*** > 2 agents	Assess risk of hypoglycaemia	Review diabetes regimen
on sulphonylureas* or insulin	High risk of hypoglycaemia	Review sulphonylurea / insulin dose before adding SGLT2 inhibitor*
HbA1c 41-58 ***and*** on ≤ 2 antidiabetic agents (except sulphonylureas/insulin)	Add SGLT2 inhibitor to existing therapy	No additional requirements
HbA1c 58 - 78	Add SGLT2 inhibitor to existing therapy	Review diabetes regimen due to poor control
HbA1c >78	Discuss with diabetes specialist	Review diabetes regimen as may require insulin
NOTE: If eGFR < 45ml/min there may be little effect on diabetic control therefore, dose reductions may not be necessary		
If in doubt, discuss with patient's diabetes specialist *Sulphonylureas e.g. gliclazide, glipizide		

- If clinically appropriate start **dapagliflozin 10mg daily or empagliflozin 10mg daily (specialist to specify)**
- For use in severe liver impairment:
  - Start dapagliflozin at 5mg daily, increasing to 10mg daily if tolerated – **discuss with heart failure specialist**
  - Do **not** use empagliflozin in severe liver impairment
- Document indication for SGLT2 inhibitor clearly to prevent confusion when monitoring glycaemic targets

Monitoring

- Reassess tolerability and volume status in 2-4 weeks and consider diuretic adjustment if necessary
- When transferring responsibility to Primary care consider timeline for availability of clinic letter and bloods. Consider if 2nd review is warranted by the initiating clinician
- A transient rise in creatinine (up to 20%) is expected in the first 2 weeks which should not lead to premature discontinuation
- Renal function should be checked at least 6 monthly according to heart failure guidelines accounting for other medicines the patient is taking including ACE inhibitors or MRA. See NICE NG106: Chronic Heart Failure in Adults.

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GP communication letter – Sacubitril/valsartan

Dear _____

Re: *Affix patient sticker: Patient Name Address DOB NHS Number*

Your patient has been identified by the Heart Failure team as a suitable candidate for the new first in class heart failure drug sacubitril/valsartan (Entresto®).
This drug was launched in December 2015 for adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction, and NICE TA388 was published in April 2016. Following a consultation, your patient has agreed to start taking this drug.

- This drug is now being used **IN PLACE OF (not in addition to)** an ACE inhibitor or ARB. Concurrent treatment is contraindicated/not recommended due to the risk of angioedema.
- **Your patient was advised to stop taking their ACEI/ARB 48 hours before starting sacubitril/valsartan.**
- **Please ensure your patient no longer receives an ACEI/ARB.**
- **Prescribing records should be updated to reflect the fact that this drug is being prescribed and supplied by the hospital/Community Heart Failure Team until you are otherwise notified.**

The following steps have been taken to ensure a safe transition onto this new drug;

- Your patient has been prescribed sacubitril/ valsartan …….mg/…….mg twice daily.
- Your patient was instructed to stop their ACEI/ARB on …… and commence sacubitril/valsartan on ……..
- The initiation of this drug is being managed by the Heart Failure team. Details of patient recruitment can be found on the Cheshire & Merseyside Strategic Clinical Networks (CMSCN) website**.**
- After initiation there will be a period of stabilisation and treatment optimisation, during which your patient will be monitored by the Heart Failure team. Prescribing and monitoring will be kept with the Heart Failure Team under advice from the hospital. Once the patient is stabilised, I would kindly ask you to continue to prescribe this drug. The Heart Failure Team will communicate this with you in writing.
- 3 copies of this letter have been given to your patient (one for themselves, one for you and one for their community pharmacy).
- The patient has been given an alert card to carry with them.
- Please refer to the sacubitril/valsartan prescribers information sheet https://www.westcheshireccg.nhs.uk/document_uploads/Guidelines/Entrestoprescribersinformationsheetv1_20160726.pdf and the SPC for key information you will need when prescribing this drug.

If you have any questions please contact your local Heart Failure team.

Kind Regards

_____

Under the supervision of a Consultant Cardiologist

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Sacubitril/valsartan (Entresto®) Information Sheet

Sacubitril/valsartan should always be prescribed using the generic name to avoid concomitant prescribing of ACEI or ARB. Initiate as per algorithm 48 hours after stopping the ACEI/ARB*

*A 48 hour washout is not required when switching from an ARB but was determined locally to avoid confusion

What is it?

Sacubitril/valsartan (Entresto®) is a combination drug containing valsartan and sacubitril. Valsartan is an angiotensin II receptor blocker (ARB). Sacubitril is a prodrug which is metabolised to the active neprilysyn inhibitor. Neprilysin breaks down endogenous vasoactive peptides. By inhibiting the breakdown of peptides, there is thought to be a reduction of neurohormal activiation, vascular tone, cardiac fibrosis and hypertrophy and sodium retention.

Who can prescribe it and how should it be initiated?

- Treatment with sacubitril/valsartan should be initiated by a Heart Failure (HF) specialist (defined as a Cardiologist, GP with specialist interest in Cardiology (GPwSi) Cardiology, nurse or pharmacist working in the Community or Hospital Heart Failure Team) with access to a multidisciplinary Heart Failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE guidance on chronic heart failure.[1] Please refer to the Strategic Clinical Networks sacubitril/valsartan treatment algorithm for more information.

- A patient information leaflet will be supplied by the Cardiologist or Heart Failure specialist nurse/pharmacist when identified as a suitable patient. The HF specialist initiating in clinic will provide the patient with 3 copies of the GP letter WITH START/STOP DATES COMPLETED (copy for patient, GP and community pharmacy). The HF specialist must send a clinic letter to the GP immediately. The template patient information and GP communication letters have been produced by the North West Coast Strategic Clinical Network & Senate and adapted for local use and should be used.

- The GP should ensure any angiotensin-converting enzyme inhibitor (ACEI) or ARB is discontinued from the repeat prescription and clearly record that the patient is receiving sacubitril/valsartan, as a hospital initiated medication, in the patients Summary Care Record on EMIS.

- Following initiation by the Cardiologist/GPwSi/HF specialist, prescribing and monitoring will be undertaken by a specialist Heart Failure nurse or pharmacist until the patient is stable on the maximum tolerated dose. Once this is achieved, the GP will continue prescribing and monitoring following clear and comprehensive communication from the Heart Failure team. The patient must receive an adequate supply of medication to allow a safe transfer of prescribing to the GP.

- Always prescribe clearly as;
  - Sacubitril 24mg/valsartan 26mg
  - Sacubitril 49mg/valsartan 51mg
  - Sacubitril 97mg/valsartan 103mg
  - Do **not** prescribe the dose as 50mg, 100mg or 200mg.
  - Do **not** prescribe or refer to by brand name. The routine use of generic sacubitril/valsartan is an additional safety prompt to prescribers that the patient is receiving a valsartan-containing treatment and therefore must not be prescribed concomitant ACEI or ARB.

What is the indication?

Sacubitril/valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:

- With New York Heart Association (NYHA) class II to IV symptoms **and**
- With severe left ventricular systolic dysfunction on ECHO (EF≤35%) **and**
- Who are already taking a stable dose of ACEI or ARBs.

Patients being considered for sacubitril/valsartan should be on stable heart failure therapy*.

*Optimal therapy is defined as beta blocker, mineralocorticoid receptor antagonist and ACE/ARB titrated to maximum tolerated dose. (Current NICE 2018 chronic heart failure pathway positions Sacubitril/Valsartan as a second line specialist option)

Key Groups in whom sacubitril/valsartan should especially (but not exclusively) be considered as an alternative to ACEI/ARB therapy include;

- NYHA class II or III
- Recent hospitalisation for heart failure (within last 6 months).

The following patients should not be considered for sacubitril/valsartan;

- ACEI/ARB naïve
- ARB intolerant (ACEI intolerant should try ARB first)
- Serum potassium >5.4mmol/Litre (consider if potassium binders could be initiated)
- End stage renal disease
- CrCl /eGFR <30mls/min (local decision - these patients were excluded from the trial)
- Systolic blood pressure <100mmHg
- Severe hepatic impairment
- A left ventricular ejection fraction >35%.

What is the dose?

- The recommended starting dose is sacubitril 49mg/valsartan 51mg **TWICE** daily. Locally, most patients will be started on the reduced dose of 24mg/26mg twice daily due to an expected fall in blood pressure.
- The dose should be doubled every 2 to 4 weeks to the recommended target dose of sacubitril 97mg/valsartan 103mg twice daily, as tolerated by the patient.
- Tablets should be swallowed with a glass of water and can be taken with or without food.

A **reduced** starting dose of 24mg/26mg **TWICE** daily with a slow dose titration (doubling every 3 to 4 weeks) should be considered for patients with:

- Patients who were taking a low dose of ACEi/ARB
- Systolic blood pressure ≥100 to 110mmHg
- Moderate renal impairment (eGFR 30-60ml/min/1.73m^2). Note patients with severe renal impairment (eGFR <30ml/min/1.73m^2) should be avoided (local decision - these patients were excluded from the trial)
- Moderate liver impairment (Child-Pugh B classification or with AST/ALT greater than twice the upper limit of normal range) used with caution due to limited clinical experience.

If patients experience tolerability issues (systolic BP ≤95mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medication, temporary down-titration or discontinuation of sacubitril/valsartan is recommended.

What monitoring is required?

Blood pressure, heart rate, renal function (including potassium) and liver function should be checked prior to initiation. Blood pressure, heart rate, renal function (including potassium) and adherence to medication should be checked before and after each dose titration and then yearly (or sooner if required).

B-type natriuretic peptide (BNP) is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate.

What should we be cautious about with this drug?[2]

- **ACEI or ARB therapy should be discontinued 48 hours before starting sacubitril/valsartan.**
- Symptomatic or severe asymptomatic hypotension. Not recommended if SBP <100mmHg.
- Serum potassium levels >5mmol/l. Not recommended if >5.4mmol/l.
- Renal artery stenosis
- Renal impairment - eGFR 30-60ml/min/1.73m^2.
- Hepatic impairment - Child-Pugh B
- Dehydration
- NYHA class IV – limited evidence of use
- Drug interactions – see below

Are there any interactions? [2]

(Note: Not an exhaustive list – please refer to SPC for full details)

Drug / Drug class	Recommendation
ACEIs	• Avoid concurrent use and allow a washout period of 48 hours when switching between ACEI and sacubitril/valsartan treatment due to the risk of angioedema
ARBs	• Avoid prescribing any additional ARBs as sacubitril/valsartan already contains the ARB valsartan
Aliskiren	• Avoid concurrent use due to a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function
Potassium-sparing diuretics, mineralocorticoid antagonists	• Monitoring of serum potassium is recommended

(spironolactone, eplerenone), potassium supplements or salt substitutes, or any agent that increases potassium	
Statins	• Sacubitril/valsartan can increase the plasma concentration of atorvastatin and its metabolites. Caution should be exercised when co-administering statins
Phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil, tadalafil, vardenafil)	• Concomitant use can result in a significant reduction in blood pressure after a single dose. Therefore caution should be exercised if a PDE5 inhibitor is initiated in patients on sacubitril/valsartan.
Nitrates (e.g., nitroglycerine)	• Co-administration with a nitrate was associated with a reduction in heart rate of 5bpm. In general no dose adjustment is required
NSAIDs including cyclo-oxygenase-2 (COX-2) inhibitors	• Concomitant use can worsen renal function; therefore if use of Sacubitril/Valsartan and an NSAID is required, close monitoring of renal function is advised
Lithium	• Although sacubitril/valsartan and lithium interactions have not been investigated, given that ACEI and ARB can cause reversible increases in lithium levels and toxicity, the use of sacubitril/valsartan and lithium is not recommended
Metformin	• Sacubitril/valsartan can reduce the plasma concentration of metformin. The clinical relevance of these findings is unknown. Therefore, when initiating therapy in patients receiving metformin, the clinical status of the patient should be monitored
Rifampicin, ciclosporin, tenofovir, cidofovir or ritonavir	• May increase systemic exposure of sarcubitril active metabolite or valsartan therefore patient should be monitored closely

What are the side-effects?[2]

(Note: For a full list of side effects, please consult the SPC)[2]

In clinical trials the most commonly reported adverse reactions for sacubitril/valsartan were:

a) **Hypotension** (reported in 17.6% of patients). It is recommended to review and correct volume and or salt depletion prior to starting treatment. If hypotension occurs during treatment, review patients' medication and consider adjusting those that are contributing to low blood pressure, or review the dose of sacubitril/valsartan, which may need to be reduced or discontinued.
b) **Hyperkalaemia** (reported in 11.6% of patients). Serum potassium should be monitored periodically especially in high-risk patients (e.g., renal impairment, diabetes, hypoaldosteronism or receiving medicines that increase potassium).
c) **Renal impairment** (reported in 10% of patients). Renal function should be closely monitored and may need to dose adjust or discontinue sacubitril/valsartan as indicated. Note: safety monitoring criteria in PARADIGM-HF excluded patients if eGFR declined > 35% within 2 weeks after initiation.
d) **Angioedema** (reported in 0.5% of patients). Sacubitril/valsartan should be discontinued if angioedema occurs and patient given the appropriate therapy and monitored for airway compromise.

Any contra-indications?[1]

- Hypersensitivity to the active substances or to any of the excipients
- Sacubitril/valsartan must not be administered until 48 hours after discontinuing ACEI/ARB therapy and if sacubitril/valsartan is to be stopped, an ACEI/ARB must not be initiated until 48 hours after discontinuation of sacubitril/valsartan therapy.
- Concomitant use with any ACEI/ARB as the combination drug contains valsartan (ARB).
- Known history of angioedema related to previous ACEI or ARB therapy
- Hereditary or idiopathic angioedema
- Systolic blood pressure (SBP) <100mmHg
- End-stage renal disease
- Serum potassium >5.4 mmol/L
- Severe hepatic impairment, biliary cirrhosis and cholestasis (Child-Pugh C)
- Concomitant use with aliskiren in patients with diabetes mellitus. Also avoid concomitant use with aliskiren in patients with renal impairment (eGFR <60ml/min/1.73 m^2)
- Pregnancy and/or breastfeeding

Can it go in a blister pack?

Use of sacubitril/valsartan in a blister pack is not recommended in the SPC and would therefore be off licence and is not recommended by Novartis. No studies on storing sacubitril/valsartan in dosette boxes have been conducted. There have been stability studies conducted in so called 'open dish' conditions, where tablets were exposed to an ambient temperature (25°C) and 60% relative humidity without any packaging, and all tablets were found to be stable for at least 3 months under those conditions.[3]

References:

1. NICE NG106. Chronic heart failure in adults: management. Sept 2018.
2. SPC- Entresto®. http://www.medicines.org.uk/emc/ accessed 25/5/16
3. Information provided upon request from Novartis Pharmaceuticals UK Medical Information Department

Patient Information leaflet (prior to starting Sacubitril/Valsartan (Entresto®)

Why have we contacted you?

Your doctor, heart failure nurse or heart failure pharmacist has already briefly spoken to you about this new tablet to help treat your heart failure. This leaflet provides further written information to help you make a decision whether or not you want to proceed and change over from one of your current heart failure tablets to this new one.

What is this new tablet?

This treatment belongs to a new class of medicine called angiotensin receptor neprilysin inhibitors (ARNIs).

Sacubitril/Valsartan is a tablet that needs to be taken twice a day, roughly 12 hours apart. Most people take the tablet first thing in the morning and in the early evening.

It has been specifically designed for people with heart failure. The medicine works in two ways to help improve the heart's ability to pump blood round the body:

- It increases the body's natural defences against heart failure.
- It blocks the body's natural system which has a harmful effect on the heart.

This treatment may not be the only medication you are taking for heart failure. If you are currently prescribed either of the types of treatment below, you will need to stop taking these 48 hours before you start Sacubitril/Valsartan (Your doctor will tell you **when** and **how** to do this when you see them):

- Angiotensin Converting Enzyme Inhibitors (ACEI) (the name of these medicines all end in 'pril' e.g. ramipril, Lisinopril, captopril, enalapril)
- Angiotensin Receptor Blockers (ARB) (the name of these medicines all end in 'sartan').

Are there any side effects with this new tablet?

Patients taking this medicine generally found that side effects, if present, were manageable. The most common side effects you may notice include light headedness due to a reduction in blood pressure, high potassium in your blood or kidney impairment.

A complete list of all known side effects is available in the Product Information Leaflet provided with your medicine.
If you do experience something that worries you, you should talk to your heart failure nurse doctor or pharmacist, as they will be able to offer you the best advice.

Is it better than the tablets I take at the moment?

Sacubitril/Valsartan was compared to Enalapril (an ACE inhibitor) in a large clinical trial. The results showed an improvement for heart failure patients. Your doctor or heart failure specialist nurse can give you more details when you come to see them.

Do I have to change to this new drug?

No. If you decide after speaking to your doctor or nurse and reading this leaflet that you would prefer to carry on taking your usual heart failure medicines that is absolutely fine.

What will happen next?

Your heart failure nurse will make an appointment for you to be considered for Sacubitril/Valsartan. We will then discuss in more detail what you need to do.

What do I do if I want more information?

If you want more information *before* you decide to change to this new tablet please feel free to ask when you come in for your appointment or call to speak to your heart failure nurse or pharmacist.

If you want more information *after* you start taking this new tablet simply call your heart failure nurse or speak to the pharmacy department.