Interface Prescribing Subgroup
SACUBITRIL/VALSARTAN (ENTRESTO®) HEART FAILURE INFORMATION FOR PRIMARY CARE

IF YOU HAVE RECEIVED A COMMUNICATION FROM A HEART FAILURE CLINIC THAT SACUBITRIL/VALSARTAN HAS BEEN COMMENCED, PLEASE STOP ANY ACEI OR ARB.

RAG List Status
Sacubitril/Valsartan (Entresto®) is classified as a GREEN (following specialist initiation) drug by the Greater Manchester Medicines Management Group.

What is it?
Sacubitril/Valsartan is an angiotensin receptor neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan).

NICE Guidance
NICE TA388: Sacubitril/Valsartan is recommended by NICE 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 a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of ACE inhibitors or angiotensin II receptor-blockers (ARBs).

Treatment with Sacubitril/Valsartan should be started by a heart failure specialist 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's guideline on Chronic Heart Failure in Adults: Management.

When should GPs be asked to prescribe?
GP will only prescribe when patient has been stabilised on **maintenance** dose for 2-3 weeks by specialist clinic and the patient meets the NICE TA criteria.

Preparations available
Sacubitril/Valsartan 24 mg/26 mg film-coated tablets (Entresto®)
Sacubitril/Valsartan 49 mg/51 mg film-coated tablets (Entresto®)
Sacubitril/Valsartan 97 mg/103 mg film-coated tablets (Entresto®)
N.B. For costs reasons prescribe the strength that matches the dose required. Do not double up on a strength to get the dose required.

Dosage and Administration
Patients will be asked to stop their ACE inhibitor or angiotensin receptor blocker two days prior to starting their Sacubitril/Valsartan prescription.

Initiation of the drug is from a specialist clinic at a dose of 100mg bd (49/51mg). If patients are receiving low doses of ACE inhibitors OR have previously not been on an ACE inhibitors or ARB then they will be started upon 50mg bd (24/26mg).
The dose will be uptitrated to 200mg bd (97/103mg or 100mg bd or 49/51mg) two to three weeks following their initial prescription after review in the specialist clinic providing there is no deterioration in renal function.

The patient will be issued with a higher dose of Sacubitril/Valsartan as their maintenance and given a further two to three weeks supply from the hospital.

Sacubitril/Valsartan can be taken with or without food. The film-coated tablet should be swallowed whole with a glass of water. If a dose is missed, the patient should take the next dose at the scheduled time.

Sacubitril/Valsartan should not be co-administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. The valsartan contained within Entresto® is more bioavailable than the valsartan in other marketed tablet formulations

Dose Modifications

Renal Impairment	Hepatic Impairment
No dose adjustment is recommended for patients with mild renal impairment	No dose adjustment is recommended for patients with mild hepatic impairment
Moderate renal impairment (eGFR 30-60ml/min/1.73 m^2): a starting dose of 24 mg/26 mg twice daily should be considered	Moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than 2x ULN: recommended starting dose is 24 mg/26 mg twice daily
Severe renal impairment (eGFR <30 ml/min/1.73 m2): use with caution and a starting dose of 24 mg/26 mg twice daily is recommended.	Contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

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Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed (refer to SPC).
- Concomitant use with ACE inhibitors.
- Angioedema related to previous ACE inhibitor or ARB therapy OR hereditary or idiopathic angioedema.
- Patients with severe hepatic impairment, biliary cirrhosis or cholestasis.
- Patients with end stage renal failure.
- 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)
- Pregnant or breastfeeding patient.

Cautions

- Hypotension. Treatment should not be initiated unless SBP is ≥100 mmHg. When initiating therapy or during dose titration, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of Entresto® is recommended - see SPC for further information
- Hyperkalaemia - Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l. If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.
- Caution in patients with renal artery stenosis and monitoring of renal function is recommended.
- Caution should be exercised when initiating in patients with NYHA functional classification IV due to limited clinical experience in this population.
- Clinical experience is limited in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range.

What are the main side-effects?

The most commonly reported adverse reactions with Sacubitril/Valsartan are hypotension, hyperkalaemia and renal impairment. Reported adverse events are generally in line with that reported for other medicinal products acting on the renin angiotensin-aldosterone system

Drug Interactions

- ACEI or Aliskerin - Do not take with Sacubitril/Valsartan.
- Entresto® contains valsartan, and therefore should not be co-administered with another ARB containing product.
- Statins – caution is advised. See SPC for further information.
- PDE-5 Inhibitors (e.g. sildenafil) – caution is advised.
- Medicines that increase the amount of potassium in the blood. These include potassium supplements, salt substitutes containing potassium, potassium-sparing medicines and heparin. Monitoring of serum potassium is recommended if Entresto® is co-administered with these agents
- NSAIDs or selective Cox-2 inhibitors. - monitoring of renal function is recommended when initiating or modifying treatment in patients on Entresto® who are taking NSAIDs concomitantly
- Lithium - combination is not recommended
- Co-administration with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised when initiating or ending concomitant treatment with such medicinal products.
- Metformin - Co-administration with metformin reduced both Cmax and AUC of metformin by 23%. The clinical relevance of these findings is unknown. When initiating therapy with Entresto® in patients receiving metformin, the clinical status of the patient should be evaluated.

Monitoring

Monitoring of Sacubitril/Valsartan is the same as for ACE inhibitors or angiotensin receptor blockers.
When initiating therapy or during dose titration with Sacubitril/Valsartan blood pressure should be monitored routinely.
Serum potassium should be regularly monitored, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists

References

SPC: Entresto film-coated tablets. Last Updated on eMC 25-Feb-2016. Novartis Pharmaceuticals UK Ltd

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