Dorset Health Technologies Forum

SHARED CARE GUIDELINE FOR PRESCRIBING EPLERENONE (INSPRA®)

INDICATION

Eplerenone is an aldosterone antagonist licensed to be used in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular ejection fraction (LVEF) ≤ 40 % and clinical evidence of heart failure after recent myocardial infarction[1]

Its license has been extended to include its use in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and LVEF ≤ 30%[1]

This is based on evidence from the EMPHASIS-HF trial. Patients were included in EMPHASIS-HF if they were at least 55 years old, had LVEF ≤ 30% or LVEF ≤ 35% in addition to QRS duration of > 130 msec, and were either hospitalized for cardiovascular reasons 6 months prior to inclusion or had a plasma level of B-type natriuretic peptide (BNP) of at least 250 pg/ml or a plasma level of N-terminal pro-BNP of at least 500 pg/ml in men (750 pg/ml in women).

Spironolactone is licensed for congestive heart failure, evidence for its use is from the Randomised Aldactone Evaluation Study (RALES).

The cardiology working group (which advises the Dorset Health Technologies Forum) considered the place of eplerenone at its meeting in May 2012 and agreed with the NPC advice that:

'Spironolactone should be the <u>first line</u> aldosterone antagonist at all stages of heart failure. This would be on the basis that spironolactone has high quality, randomised controlled trial evidence of effectiveness from the RALES study in heart failure NYHA class III or IV, established data for hyperkalaemia risks, it is likely (but not known) that spironolactone would also be effective at other stages of heart failure as well as NYHA III and IV, and it has a broad licence for congestive cardiac failure which is not restricted to any heart failure class'[2]

Spironolactone remains the first line choice aldosterone antagonist in heart failure; eplerenone should be reserved for patients unable to tolerate spironolactone, for example, due to painful gynaecomastia.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of eplerenone can be shared between the specialist and general practitioner (GP) or non-medical prescriber (NMP) in primary care. GP's are invited to participate. (Note: in this document, medical and non-medical prescribers in primary care are abbreviated as 'GP')

If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to shared care is usually explained to the patient by the doctor/NMP initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor/NMP who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed in each individual case.

- Management of chronic heart failure should be consistent with NICE Clinical Guideline no. 108.

SPECIALIST RESPONSIBILITIES	
1	To clinically assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	• to initiate treatment (although this initiation may be via verbal recommendation or request direct to the GP or Community Heart Failure Teams) • To determine need for eplerenone within licensed indication and recommendations from the Dorset Health Technologies Forum. • To seek agreement from the patient's GP to transfer responsibility for prescribing. • To monitor progress and to notify GP of any changes in the patient's condition as assessed on follow up.
3	To explain the possible side-effects of eplerenone treatment to the patient
4	Ensure that the patient knows what to do and who to contact if they experience adverse events
5	To provide the GP with appropriate prescribing information (including length of course) and any additional information requested.
6	To agree with the GP arrangements for ongoing monitoring to ensure the safe use of eplerenone. This should include responsibility for undertaking any necessary tests as mentioned above.
7	To be available for advice if the patient's condition changes and to arrange follow up in clinic at intervals to monitor the progress and review the continued use of eplerenone.
8	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
9	To ensure the patient has given informed consent to their treatment.
10	To liaise with the GP on any suggested changes in prescribed therapy / notify GP of any changes in the patient's condition as assessed on follow up.
11	To inform the GP when it is considered appropriate to discontinue treatment.

GENERAL PRACTITIONER RESPONSIBILITIES	
1	To contact the referring consultant without delay if they do not wish to enter into a shared care agreement.
2	Where appropriate initiate or continue prescriptions of eplerenone in accordance with the instructions from the consultant.
3	To monitor side effects of treatment and seek advice from the consultant if necessary.
4	To deal with general health issues of the patient.
5	To liaise with the consultant regarding any complications of treatment.
6	To check for possible drug interactions when newly prescribing or stopping concurrent medication.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he/she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	To have any required monitoring/tests carried out at regular intervals, as appropriate.
4	Share any concerns in relation to treatment with eplerenone.
5	Seek help urgently if suspected side effects appear, or otherwise unwell.

SUPPORTING INFORMATION

DOSAGE AND ADMINISTRATION

ADULTS

For post myocardial infarction heart failure patients:

Recommended maintenance dose is 50mg daily. Treatment should be initiated at 25mg once daily, increased within 4 weeks to 50mg once daily, taking into account the serum potassium level. Eplerenone should be started within 3-14 days after acute MI.

For NYHA Class II (chronic) heart failure patients:

Treatment should be initiated at a dose of 25mg daily and titrated to the target dose of 50mg daily preferably within 4 weeks, taking into account the serum potassium level.

Patients with a serum potassium of > 5.0 mmol/L should not be started on eplerenone.

Serum potassium should be measured before initiating eplerenone therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed as needed periodically thereafter.

After initiation, the dose should be adjusted based on the serum potassium level as shown in Table 1.

Table 1: Dose adjustment table after initiation

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

* EOD: Every Other Day

Following withholding eplerenone due to serum potassium ≥6.0 mmol/L, eplerenone can be re-started at a dose of 25 mg every other day when potassium levels have fallen below 5.0 mmol/L.

Dosage adjustments in specific patient populations

Children and adolescents

There is no data to recommend the use of eplerenone in the paediatric population, and therefore, use in this age group is not recommended.

Elderly

No initial dose adjustment is required in the elderly. Due to an age-related decline in renal function, the risk of hyperkalaemia is increased in elderly patients. This risk may be further increased when co-morbidity associated with increased systemic exposure is also present, in particular mild-to-moderate hepatic impairment. Periodic monitoring of serum potassium is recommended

Renal impairment

No initial dose adjustment is required in patients with mild renal impairment. Periodic monitoring of serum potassium is recommended.

Patients with moderate renal impairment (CrCl 30-60 ml/min) should be started at 25mg every other day, and dose should be adjusted based on potassium levels.

Exercise caution with use of eplerenone in patients with a CrCl <50ml/min with post MI heart failure.

Doses above 25mg daily have not been studied in patients with CrCl <50ml/min.

Patients with severe renal impairment (CrCl <30ml/min) are contraindicated.

Eplerenone is not dialysable.

Hepatic impairment

No initial dosage adjustment is necessary for patients with mild-to-moderate hepatic impairment. Due to an increased systemic exposure to eplerenone in patients with mild-to-moderate hepatic impairment, frequent and regular monitoring of serum potassium is recommended in these patients, especially when elderly.

Concomitant treatment

In case of concomitant treatment with mild to moderate CYP3A4 inhibitors, e.g. amiodarone, diltiazem and verapamil, a starting dose of 25 mg daily may be initiated. Dosing should not exceed 25 mg daily.

Eplerenone may be administered with or without food

Contraindications

- Hypersensitivity to eplerenone or any of the excipients
- Patients with serum potassium level > 5.0 mmol/L at initiation
- Patients with severe renal insufficiency (eGFR <30mL/min per 1.73m^2)
- Patients with severe hepatic insufficiency (Child-Pugh Class C)
- Patients receiving potassium-sparing diuretics, potassium-supplements or strong inhibitors of CYP 3A4 (eg itraconazole, ketoconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazodone)

- The combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) with eplerenone (triple therapy) is contraindicated. Dual therapy (ACE inhibitor or ARB with eplerenone is indicated).

Special Warnings

Hyperkalaemia: Consistent with its mechanism of action, hyperkalaemia may occur with eplerenone. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter, periodic monitoring is recommended especially in patients at risk for the development of hyperkalaemia, such as (elderly) patients with renal insufficiency and patients with diabetes. The use of potassium supplements after initiation of eplerenone therapy is not recommended, due to an increased risk of hyperkalaemia. Dose reduction of eplerenone has been shown to decrease serum potassium levels. In one study, the addition of hydrochlorothiazide to eplerenone therapy has been shown to offset increases in serum potassium.

The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). The combination of an ACE inhibitor and an ARB with eplerenone should not be used.

Impaired renal function: Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. While the data from EPHESUS in patients with type 2 diabetes and microalbuminuria is limited, an increased occurrence of hyperkalaemia was observed in this small number of patients. Therefore, these patients should be treated with caution. Eplerenone is not removed by haemodialysis.

Impaired hepatic function: No elevations of serum potassium above 5.5 mmol/L were observed in patients with mild to moderate hepatic impairment (Child Pugh class A and B). Electrolyte levels should be monitored in patients with mild to moderate hepatic impairment. The use of eplerenone in patients with severe hepatic impairment has not been evaluated and its use is therefore contraindicated.

CYP3A4 inducers: Coadministration of eplerenone with strong CYP3A4 inducers is not recommended.

Lithium, ciclosporin, tacrolimus should be avoided during treatment with eplerenone.

Lactose: The tablets contain lactose and should not be administered in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Pregnancy and Breastfeeding

Pregnancy: There are no adequate data on the use of eplerenone in pregnant women. Animal studies did not indicate direct or indirect adverse effects with respect to pregnancy, embryofoetal development, parturition and postnatal development. Caution should be exercised prescribing eplerenone to pregnant women.

Breast Feeding: It is unknown if eplerenone is excreted in human breast milk after oral administration. However, preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route developed normally. Because of the unknown potential for adverse effects on the breast fed infant, a decision should be made whether

to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions

Pharmacodynamic interactions

Potassium-sparing diuretics and potassium supplements
Due to increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving potassium-sparing diuretics and potassium supplements. Potassium-sparing diuretics may potentiate the effect of anti-hypertensive agents and other diuretics.

ACE inhibitors, angiotensin receptor blockers (ARB):
The risk of hyperkalaemia may increase when eplerenone is used in combination with an ACE inhibitor and/or angiotensin receptor blocker (ARB). A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function eg, the elderly. The triple combination of an ACE, an ARB and eplerenone should not be used.

Lithium
Drug interaction studies of eplerenone have not been conducted with lithium. However, lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Coadministration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored.

Ciclosporin, tacrolimus
Ciclosporin and tacromilus may lead to impaired renal function and increase the risk of hyperkalaemia. The concomitant use of eplerenone and ciclosporin or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are recommended when ciclosporin and tacrolimus are to be administered during treatment with eplerenone

Non-steroidal anti-inflammatory drugs (NSAIDs)
Treatment with NSAIDs may lead to acute renal failure by acting directly on glomerular filtration, especially in at-risk patients (elderly and/or dehydrated patients). Patients receiving eplerenone and NSAIDs should be adequately hydrated and be monitored for renal function prior to initiating treatment.

Trimethoprim
The concomitant administration of trimethoprim with eplerenone increases the risk of hyperkalaemia. Monitoring of serum potassium and renal function should be made, particularly in patients with renal impairment and in the elderly.

Alpha 1 blockers (e.g. prazosin, alfuzosin)
When alpha-1-blockers are combined with eplerenone, there is the potential for increased hypotensive effect and/or postural hypotension. Clinical monitoring for postural hypotension is recommended during alpha-1-blocker co-administration.

Tricyclic anti-depressants, neuroleptics, amifostine, baclofene:
Co-administration of these drugs with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.

Glucocorticoides, tetracosactide
Co-administration of these drugs with eplerenone may potentially decrease antihypertensive effects (sodium and fluid retention).

Pharmacokinetic interactions

In vitro studies indicate that eplerenone is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4 isozymes. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein.

Digoxin
Systemic exposure (AUC) to digoxin increases by 16% (90% CI: 4% - 30%) when co-administered with eplerenone. Caution is warranted when digoxin is dosed near the upper limit of therapeutic range.

Warfarin
No clinically significant pharmacokinetic interactions have been observed with warfarin. Caution is warranted when warfarin is dosed near the upper limit of therapeutic range.

CYP3A4 substrates
Results of pharmacokinetic studies with CYP3A4 probe-substrates, i.e. midazolam and cisapride, showed no significant pharmacokinetic interactions when these drugs were coadministered with eplerenone.

CYP3A4 inhibitors

Strong CYP3A4 inhibitors: Significant pharmacokinetic interactions may occur when eplerenone is coadministered with drugs that inhibit the CYP3A4 enzyme. A strong inhibitor of CYP3A4 (ketoconazole 200 mg BID) led to a 441% increase in AUC of eplerenone. The concomitant use of eplerenone with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazadone, is contra-indicated.

Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, amiodarone, diltiazem, verapamil, and fluconazole have led to significant pharmacokinetic interactions with rank order increases in AUC ranging from 98% to 187%. Eplerenone dosing should therefore not exceed 25 mg when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone.

CYP3A4 inducers: Co-administration of St John's Wort (a strong CYP3A4 inducer) with eplerenone caused a 30 % decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with stronger CYP3A4 inducers such as rifampicin. Due to the risk of decreased eplerenone efficacy, the concomitant use of strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) with eplerenone is not recommended

Antacids: Based on the results of a pharmacokinetic clinical study, no significant interaction is expected when antacids are co-administered with eplerenone.

Side Effects

Eplerenone does not cause drowsiness or impairment of cognitive function although dizziness is a side effect.

Common side effects include: hyperkalaemia, dizziness, hypotension, syncope, diarrhoea, nausea, abnormal renal function, raised blood urea, rash and cough.

This list is not exhaustive – the manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary (BNF) should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

References

1. Inspra, Summary of Product Characteristics (2012) accessed at http://www.medicines.org.uk/EMC/medicine/16746/SPC/Inspra+25mg+%26+50+mg+film-coated+tablets/

2. *National Prescribing Centre (NPC) Eplerenone▼ for patients with NYHA class II chronic heart failure accessed at http://www.npc.nhs.uk/new_medicines/cardio/heart/oth_eplerenone.php*

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