Oxfordshire Clinical Commissioning Group, Oxford University Hospitals NHS Trust and Oxfordshire Health NHS Foundation Trust
Shared Care Protocol and Information for GPs

Ranolazine: add on therapy for symptomatic treatment of patients with stable angina

This leaflet provides the necessary information and guidance for the shared care of adult patients requiring Ranolazine

This shared care agreement states how prescribing and monitoring responsibilities can be shared between the specialist and primary care. Shared care should only take place when all parties, including the patient, agree. A GP should only take on the prescribing if he/she has been provided with all the necessary information from the specialist and feels that it was within his/her competency to do so. APCO have agreed that if these conditions are met then this medicine is suitable for shared care under this protocol.

Background

Ranolazine is a new class of anti-anginal therapy. The exact mechanism of action is largely unknown. Ranolazine may have some anti-anginal effects by inhibition of the late sodium inward current in cardiac cells. This reduces intracellular sodium accumulation and consequently decreases calcium overload. Ranolazine is considered to reduce intracellular ionic imbalances during ischaemia. The reduction in cellular calcium overload is expected to improve myocardial relaxation and decrease left ventricular stiffness. Unlike other anti-anginal agents ranolazine does not significantly alter heart rate or blood pressure.[1]

Treatment of angina is based on a step wise increment of treatment options with beta blockers or calcium channel blockers offered as first-line treatment. If either a beta or calcium channel blocker does not control symptoms consider the other option or using both drugs together. If both beta blockers and calcium channel blockers are not tolerated, or do not control symptoms a third line agent may be considered either as monotherapy (if either are not tolerated) or as add-on therapy. Third line agents include: long-acting nitrate, nicorandil, ivabradine or ranolazine. To date there are no large randomized trials that address treatment strategies in patients with chronic angina who are refractory to more than 2 anti-anginal agents.[2]

Indications

Ranolazine is licensed for add-on therapy for the treatment of patients with stable angina who are inadequately controlled or intolerant to first line anti-anginal therapies (such as beta-blockers and/or calcium channel blockers).[1,2] In clinical practice ranolazine will be restricted to those patients who have tried a combination of at least 2 or more anti-anginal therapies (at adequate doses) and have on-going symptoms. Ranolazine may be suitable for a small number of patients who do not have significant co-morbidities or concomitant medication that would preclude its use.

Prescribing Information

Ranolazine therapy is initiated by either a consultant cardiologist or a consultant nurse specialist and continued by the GP. Ranolazine is available as 375mg, 500mg and 750mg modified release tablets. The tablets should be swallowed whole and may be taken with or without food.

Dose regimen:[1]

- Initial dose is 375mg twice daily.
- Increase after 2 to 4 weeks according to patient response to 500mg twice daily
- The dose can be further titrated to a maximum dose of 750mg twice daily

Careful dose titration is required in the following groups of patients:

- Patients with mild to moderate renal impairment (eGFR 30 - 80ml/min)
- Patients with mild hepatic impairment

- Elderly patients (aged 75 years and greater) and those with low body weight (less than 60kg)
- Patients with moderate to severe congestive heart failure (CHF), (NYHA class III- IV)

See below for contra-indications

Adverse Effects

Common adverse effects include dizziness, headache, nausea or vomiting and constipation and often develop within the first 2 weeks of therapy. If a patient experiences treatment related adverse events the dose should be reduced to 500mg or 375mg twice daily. If adverse effects do not resolve with dose reduction, treatment should be discontinued. Adverse effects may occur more frequently in the elderly, those with low body weight and those with renal impairment.

Contra-indications/Cautions

Ranolazine is contra-indicated in the following groups of patients:

- Patients with severe renal impairment (eGFR less than 30ml/min)
- Patients with moderate to severe hepatic impairment
- Patients taking potent CYP3A4 inhibitors (see below)
- Patients taking Class Ia (e.g. quinidine) or Class III (e.g. sotalol) antiarrhythmics other than amiodarone

Ranolazine should be used with caution in the following groups of patients:

- Patients taking moderate CYP3A4 inhibitors and P-glycoprotein inhibitors (see below)
- Patients with mild to moderate renal impairment
- Patients with a congenital or a family history of long QT syndrome or patients with known acquired QT interval prolongation
- The elderly and those with low body weight
- Patients with moderate to severe CHF

If ranolazine is used in patients with a combination of several of these factors monitoring of adverse events should be frequent and the dose reduced as appropriate.

Pregnancy and Lactation

Ranolazine should not be prescribed during pregnancy or breast feeding.

Drug Interactions

Ranolazine is metabolised by the cytochrome CYP3A4 and partially by CYP2D6. It is also a substrate for P glycoprotein. The main drug interactions are listed below please refer to SPC or BNF for further information. (Ranolazine SPC)

Plasma concentrations of ranolazine increased by:

- Ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, clarithromycin and grapefruit juice - **avoid concomitant use**.
- Diltiazem, verapamil, erythromycin and fluconazole – avoid doses above 500mg twice a day unless specifically advised by a cardiologist.

Plasma concentrations of ranolazine reduced by:

- Rifampicin, phenytoin, carbamazepine, St John's Wort – **avoid concomitant use**.

Ranolazine increases plasma concentrations of simvastatin, restrict simvastatin dose to 40mg.

Digoxin plasma levels are increased by ranolazine, monitor digoxin levels with concomitant use.

Avoid concomitant use of ranolazine with sotalol and disopyramide.

Concomitant treatment of ranolazine with other medicines known to prolong the QTc interval may increase the risk of ventricular arrhythmias, e.g. antihistamines (e.g. terfenadine, astemizole) certain antiarrhythmics, erythromycin and tricyclic antidepressants.

Monitoring
Pre-treatment:

- Recent ECG
- Urea, electrolytes, renal function and hepatic enzymes

Ongoing treatment: No specific monitoring required but routine assessment of renal function and hepatic enzymes as part of normal patient care.

Patient Information Leaflet
Patients should be supplied with the manufacturer's information leaflet and patient alert card.

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

A) Aspects of care for which the Hospital Consultant is responsible:

- Initiation of ranolazine therapy and continuation of prescribing for the first month of therapy.
- Write to the GP requesting shared care and outline shared care protocol criteria giving specific information about dose titration of ranolazine.
- Liaise with GP regarding changes in disease management, drug dose, and missed clinic appointments.
- Ensure clinical supervision of the patient is done by follow-up as appropriate.
- Ensure the patient understands the nature and complications of ranolazine therapy and their role in reporting adverse effects promptly.
- Provide clear instruction to GP on when therapy needs to be referred back to specialist.
- Be available to give advice to GP and patient.

B) Aspects of care for which the GP is responsible

- Prescribe ranolazine according to a written protocol.
- Advise the Hospital Consultant of any clinical changes or adverse effects where appropriate.
- Monitor for adverse effects as detailed above.
- Be aware of any specific drug interactions with ranolazine when prescribing new drugs.

C) Aspects of care for which the Patient is responsible:

- Ensure they bring a list of current medication to every hospital visit.
- Report any adverse effects to their GP and/or consultant
- Attend for regular monitoring as requested by GP / Hospital consultant.

Contact Details
Cardiac Registrar on call: 01865 741166 bleep 4205
Specialist Cardiac Pharmacist: 01865 857881 or 01865 741166 and ask for bleep 1852

Annual Cost of Medicine in Primary Care:
BNF costs: £48.98 per month (all strengths)

Number of New Patients per Annum: Approximately 12 patients per year.

References:

1. Ranexa. Summary of Product characteristics accessed via eMC, last updated 28/06/2011.
2. Management of stable angina. NICE clinical guideline 126. (July 2011).