Dorset Medicines Advisory Group

**SHARED CARE GUIDELINE FOR PRESCRIBING RANOLAZINE (RANEXA®) FOR THE TREATMENT OF SYMPTOMATIC STABLE ANGINA PECTORIS.**

**INDICATION**

Ranolazine is an antianginal which is thought to exhibit its effects by inhibition of sodium current in cardiac cells. The reduction in accumulated sodium and consequential decrease in ion imbalance within cardiac cells during periods of ischaemia is thought to cause a net decrease in the left ventricular diastolic stiffness. The antianginal effects are therefore expected without a significant decrease in blood pressure and heart rate.

Ranolazine (Ranexa®) is licensed for use in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies. Its use should be reserved to patients with limiting angina despite aggressive antianginal therapy with ≥2 conventional agents (Beta blocker, calcium channel blocker, nitrate, nicorandil and ivabradine) with the following provisos:

1. There is confirmed coronary artery disease (CAD)
2. The options for revascularization are limited due to patient co-morbidity or not possible due to a lack of treatable target vessels
3. Conventional antianginal treatment has been exhausted or is contra-indicated
4. The heart rate is <65/minute or cannot be reduced despite aggressive rate controlling agents and the patient is still significantly symptomatic

**AREAS OF RESPONSIBILITY FOR SHARED CARE**

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of ranolazine can be shared between the specialist setting and the patient’s GP (if different). GPs are invited to participate. 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. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor 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 to continuation in each individual case. The shared care guideline and amber position of ranolazine will give provision for GP continuation of ranolazine provided that the following conditions are met:

1. Ranolazine is indicated in accordance with above guidance
2. The prescription is started in secondary care and there is confirmation of a clinical response either by further clinic follow up or telephone contact with the patient.
3. Patients with angina are managed in line with NICE Clinical Guideline no. 126 (Management of patients with stable angina).
4. Ranolazine is a “black triangle” drug. The MHRA therefore asks that all suspected reactions (including those not considered to be serious) are reported through the Yellow Card Scheme.
**Specialist Responsibilities**

1. To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.

2. Where appropriate:
   - to initiate treatment
   - obtain agreement from the patient’s GP to continue the ongoing prescribing
   - Monitor and assess the patient at 4, 8 and 12 weeks post initiating ranolazine and ascertain patient response to therapy and titrate dose accordingly as tolerated.
   - If positive response achieved, specialist to request that the GP continues prescribing ranolazine thereafter within the parameters of the shared care agreement

3. To provide the GP with appropriate prescribing information and any additional information requested.

4. To be available for advice if the patient’s condition changes.

5. To ensure that procedures are in place for the rapid re-referral of the patient by the GP.

6. To ensure the patient has given informed consent to their treatment.

7. To liaise with the GP on any suggested changes in prescribed therapy.

**General Practitioner Responsibilities**

1. Initially, to refer the patient for specialist advice.

2. Where appropriate, to continue to prescribe ranolazine as part of a shared care arrangement.

3. Monitor the patient’s condition and discuss with Specialist as appropriate

4. To manage general health issues of the patient.

5. Monitor concordance with therapy

**Patient’s role (or that of carer)**

1. Report to the specialist or GP if he or she does not have a clear understanding of the treatment.

2. Attend appropriate GP and other follow up appointments

3. Share any concerns in relation to treatment with ranolazine

4. Use written and other information on the medication

5. Seek help urgently if side effects are suspected, or are otherwise unwell.

**SUPPORTING INFORMATION**

**Dosage and Administration**

Ranolazine (Ranexa) is available as 375mg, 500mg and 750mg tablets. Tablets must be taken orally twice daily, once in the morning and once in the evening. Tablets should be swallowed whole and not crushed, broken, or chewed. They may be taken with or without food.

The usual recommended starting dose of ranolazine for symptomatic treatment of patients with stable angina pectoris is 375mg twice a day. After 4 weeks the dose should be titrated to 500mg twice a day according to the patient’s response and further titrated to 750mg twice a day as tolerated. If a patient experiences treatment-related adverse events (e.g. dizziness, nausea, or vomiting), down-titration of ranolazine (Ranexa) to 500 mg or 375 mg twice daily may be required. If
symptoms do not resolve after dose reduction, treatment should be discontinued. After this titration phase (3 months) the GP can then continue treatment under the shared care agreement as appropriate.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Moderate or severe hepatic impairment.
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone)
- Concomitant administration of Class IA (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone.

Cautions

- **Concomitant treatment with CYP3A4 and P-glycoprotein (P-gp) inhibitors:** Careful dose titration is recommended in patients treated with moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, erythromycin) or P-gp inhibitors (e.g. verapamil, ciclosporin)
- **Renal impairment:** Careful dose titration is recommended in patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min).
- **Hepatic impairment:** Careful dose titration is recommended in patients with mild hepatic impairment
- **Elderly:** Dose titration in elderly patients should be exercised with caution as they may have increased ranolazine exposure due to age-related decrease in renal function. The incidence of adverse events was higher in the elderly
- **Low weight:** The incidence of adverse events was higher in patients with low weight (≤ 60 kg). Dose titration in patients with low weight should be exercised with caution.
- **Congestive heart failure (CHF):** Dose titration in patients with moderate to severe CHF (NYHA Class III–IV).

Side effects

Common side effects (1/100 to < 1/10) include:

- Dizziness
- Headaches
- Constipation
- Nausea and vomiting
- Asthenia

Interactions

- Ranolazine is a substrate of cytochrome CYP3A4. Inhibitors of CYP3A4 increase plasma concentrations of ranolazine. The potential for dose-related adverse events may also increase with increased plasma concentrations.
- Ranolazine is a substrate for P-gp. Inhibitors of P-gp increase plasma levels of ranolazine. Down-titration of Ranolazine may be required.
• **CYP3A4 inducers:** decrease ranolazine steady-state concentrations. Initiation of treatment with Ranolazine should be avoided during administration of inducers of CYP3A4 (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort)

• **CYP2D6 inhibitors:** Ranolazine is partially metabolised by CYP2D6; therefore, inhibitors of this enzyme may increase plasma concentrations of ranolazine.

Ranolazine is a moderate to potent inhibitor of P-gp and a mild inhibitor of CYP3A4, and may increase plasma concentrations of P-gp or CYP3A4 substrates. Tissue distribution of drugs which are transported by P-gp may be increased. Dose adjustment of sensitive CYP3A4 substrates (e.g. simvastatin, lovastatin) and CYP3A4 substrates with a narrow therapeutic range (e.g., ciclosporin, tacrolimus, sirolimus, everolimus) may be required as Ranolazine may increase plasma concentrations of these drugs.

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

**Drug costs:**

- Ranolazine (Ranexa®) 375mg Modified Release Tablets x 60 £48.98
- Ranolazine (Ranexa®) 500mg Modified Release Tablets x 60 £48.98
- Ranolazine (Ranexa®) 750mg Modified Release Tablets x 60 £48.98

Prices referenced from Drug Tariff accessed November 2016

**References**

1. Ranolazine Summary of Product Characteristics last updated December 2015, accessed November 2016:
2. NICE Guidelines for stable angina: [https://www.nice.org.uk/guidance.CG126](https://www.nice.org.uk/guidance.CG126)

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**Reviewed** Cardiology Working group

**Next Review** November 2018 or before, in light of new information
Algorithm for use of ranolazine

1st line
Cardio selective B-blocker (BB)
E.g. Bisoprolol

2nd Line
Long acting nitrate / nicorandil or
dihydropyridine CCB e.g. amlodipine in BB patients

3rd line
>65/minute in sinus rhythm use ivabradine

<65/minute or atrial fibrillation use ranolazine

Non dihydropyridine Calcium channel blocker (CCB)
E.g. diltiazem/verapamil

Aspirin 75mg od
Simvastatin 40mg od
Treat risk factors

Consider revascularisation options

Resting heart rate

Limiting angina

Cardio selective B-blocker (BB)
E.g. Bisoprolol

Non dihydropyridine Calcium channel blocker (CCB)
E.g. diltiazem/verapamil

Aspirin 75mg od
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Treat risk factors

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