BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Ranolazine (Ranexa) prolonged-release tablets
Amber *one month*	
Indication	Ranolazine is indicated in adults as an adjunct for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerance to first-line antianginal therapies (such as beta-blockers or calcium channel blockers)
Speciality / Department	Cardiology
Trust(s)	North Bristol NHS Trust
	University Hospitals Bristol NHS Foundation Trust
	Weston Area Health NHS Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed and any relevant dosing information)*	The recommended initial dose of ranolazine is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice daily. Consult the specialist if symptom improvement is not achieved with the maximum dose.
Route and formulation	Oral, prolonged release tablets
Duration of treatment	Long-term

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
1. Creatinine levels –Baseline creatinine levels will be required as ranolazine is contraindicated if creatinine clearance is < 30ml/min. Careful dose titration is recommended in patients with creatinine clearance 30 – 80ml/min.

2. Hepatic function –Baseline assessment of hepatic function should be performed as ranolazine is contraindicated in moderate to severe hepatic impairment. Careful dose titration is recommended in patients with mild hepatic impairment.

3. ECG – to confirm absence of QT interval prolongation

Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results)*

Test	Frequency	Who by	Action/management
Urea and electrolytes	Annually	GP	Discontinue and refer back to cardiologist if renal impairment with CrCl <30mL/min
Liver function tests	Annually	GP	Refer back to cardiologist in moderate to severe hepatic impairment

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNF or SPC.

Side effects and management

Side effect	Frequency/severity	Action/management
Dizziness, headache Constipation, vomiting, nausea	Common side effects (≥1/100 to <1/10)	Consider dose reduction or referral back to specialist if not tolerated. May be transient so encourage patient to persist at first presentation if not severe
Anaphylactic reactions including angioedema Angioedema, allergic dermatitis, urticaria, rash Elevated levels of hepatic enzyme Increased blood creatinine Increased blood urea Prolonged QTc interval	Rare side effects (≥1/10,000 to <1/1000)	Stop treatment and refer back to specialist Consider dose reduction if tolerated at lower dose; if not tolerated refer back to specialist

Referral back to specialist

If a patient experiences treatment-related adverse effects (e.g. dizziness, nausea or vomiting), dose reduction to 500mg BD or 375mg BD may be required. Side effects may be transient so encourage patient to persist at first presentation if not severe. Most other side effects are deemed uncommon or rare and a similar principle should be applied. If dose reduction does not resolve symptoms, then discontinue and the specialist should be informed.

See SPC for full details of uncommon and rare side effects; the principles discussed in this section can be applied to these side effects.

Section 5: Other Issues

(E.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent action for GP to take (For full list please see BNF or SPC)

Issues	**Interactions:** CYP3A4 inhibitors, CYP2D6 inhibitors and P-glycoprotein inhibitors can increase exposure to ranolazine • Caution with moderate inhibitors; e.g. diltiazem, fluconazole, erythromycin, verapamil, ciclosporin, fluoxetine, paroxetine • Contraindicated with potent inhibitors; itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromyin, telithromycin, nefazodone, grapefruit juice Concomitant use with anti-arrhythmics: • Contraindicated with Class Ia and Class III antiarrhythmics (e.g. dofetilide, sotalol; other than amiodarone, is contraindicated • Caution should be exercised with other drugs known to prolong the QTc interval CYP3A4 inducers can decrease exposure to ranolazine • Caution with rifampicin, phenytoin, phenobarbital, carbamazepine, St John's Wort) Ranolazine is a moderate to potent inhibitor of P-glycoprotein and a mild inhibitor of CYP3A4 and CYP2D6, can increase exposure to other agents • Caution with statins e.g. simvastatin, lovastatin; digoxin; metoprolol, propafenone, flecainide, tricyclic antidepressants, antipsychotics and • Caution with CYP3A4 substrates with a narrow therapeutic range (e.g. ciclosporin, tacrolius, sirolimus, everolimus) **Contraindications:** 1.Hypersensitivity to active substance or any of the excipients 2.Concomitant administration of potent CYP3A4 inhibitors (see 'Significant Drug Interactions') 3.Severe renal impairment (creatinine clearance <30mL/min) 4.Moderate-to-severe hepatic impairment 5.Concomitant administration with CYP3A4 inducers (see 'Significant Drug Interactions') **Cautions** 1. Concomitant administration of moderate CYP3A4 inhibitors or P-glycoprotein inhibitors (see 'Significant Drug Interactions' 2. Mild-to-moderate renal impairment (creatinine clearance 30-80mL/min); warrants careful dose titration 3. Mild hepatic impairment; warrants careful dose titration 4. Elderly patients; careful dose titration as higher incidence of adverse events 5. Weight ≤ 60kg; careful dose titration as higher incidence of adverse events 6. Congestive heart failure, moderate to severe heart failure (NYHA Class III to IV) 8. Patients with a history of congenital or a family history of long QT syndrome, in known acquired QT interval prolongation and in patients treated with drugs affecting the QTc interval 9. In patients with a combination of these factors, additional exposure

	increases are excepted; dose-dependent side effects are more likely to occur and additional monitoring is recommended Special Recommendations 3. Ranolazine should not be used during pregnancy unless clinically necessary, as risk for humans is unknown 4. Ranolazine should not be used when breast-feeding, as exposure in milk is unknown See Summary of Product Characteristics for full pharmacokinetic information on drug interactions
Reminder to ask patient about specific problems	Full medication history including herbal and homeopathic supplementation to fully assess for drug-drug interactions Advise not to drink grapefruit juice during treatment with ranolazine Remind patient to state they are taking ranolazine when seeing a healthcare professional for prescribing of a new medicine or if over-the-counter medications are purchased.

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Tablets should be swallowed whole and not crushed, broken or chewed
2. Tablets may be taken with or without food
3. Avoid grapefruit juice alongside treatment with ranolazine
4. Patients should be informed of the common side effects and the need to inform the prescriber if they experience any side effects
5. Patients should report any symptomatic deterioration to the prescriber. Immediate medical attention should be sought if there is a sudden worsening in frequency or severity of their angina.
6. Patients should be informed of the importance of attending for annual renal and liver function tests
7. Usage during pregnancy, breast-feeding and when trying to conceive is unknown
8. Ranolazine may affect the ability to drive and operate machinery

Section 7: Generic principles of shared care for SECONDARY CARE

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1.**
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3.**
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 2.**
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see **section 5.**

Section 8: Generic principles of shared care for PRIMARY CARE

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1.**
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1.**
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5.**

Section 10: Contact Details

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Section 11: Document Details

Date prepared	June 2019
Prepared by	Glen Cooper, Specialist Cardiac Pharmacist, University Hospitals Bristol NHS Foundation Trust Adapted from earlier draft by Jacqueline Criper, Nicola Bruce
Date approved by JFG	July 2019
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Document Identification: Version	Ranolazine SCP v 1.3

Section 12: Collaboration

All shared care protocols should be BNSSG wide where possible. Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. UHBristol Cardiologists and Specialist Pharmacist

Section 13: References

Please list references

1. Summary of Product Characteristics, Ranexa prolonged-release tablets, Menarini Farmaceutica Internazionale SRL [Last Updated March 2019]