***Amber with Guidance**= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

NHS South West Yorkshire Partnership NHS Foundation Trust

NHS Barnsley Hospital NHS Foundation Trust

NHS Barnsley Clinical Commissioning Group

Guidelines for prescribing **Ranolazine** in the Management of Stable Angina Pectoris

Introduction

Indication/Licensing information
Ranolazine (Ranexa), as recommended by NICE, is indicated 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 (such as beta-blockers and/or calcium antagonists).

Pharmacology
The mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; it also inhibits fatty acid oxidation.

Dosage and administration
The recommended initial dose of Ranozaline 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.

If treatment-related adverse events (e.g. dizziness, nausea, or vomiting) are experienced; down-titration of Ranolazine to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be *discontinued*.

Dose reduction and 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 (CrCl = 30–80 ml/min). Ranolazine is contraindicated in patients with severe renal impairment (CrCl = < 30 ml/min)

Hepatic impairment: Careful dose titration is recommended in patients with mild hepatic impairment (Child-Pugh score A). Ranolazine is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh score B-C).

Elderly: Dose titration in elderly patients should be exercised with caution due to increased Ranolazine exposure secondary 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). Therefore dose titration in these patients should be exercised with caution.

Congestive heart failure (CHF): Dose titration in patients with moderate to severe CHF (NYHA Class III–IV) should be exercised with caution.

Ranolazine is available as 375 mg, 500 mg, and 750 mg prolonged-release tablets. Ranolazine tablets should be swallowed whole and not crushed, broken, or chewed. They may be taken with or without food.

Patients should be given the Ranolazine package leaflet and the Patient Alert Card and instructed to present their Patient Alert Card and medication list to their health care professional at each visit.

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Responsibilities of Prescribers

Summary

- To prescribe and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To continue monitoring as agreed with secondary care (guideline should include details of monitoring requirements and what to do when each of the defined parameters alters).
- To refer back to the specialist where appropriate. For example:
  - Patient or general practitioner is **not** comfortable to continue with the existing regime due to either change in condition or drug side effects.
  - Advice in respect of concordance.
  - Special situations, (e.g. Pregnancy)
- Discontinue the drug as directed by the specialist if required
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme).

Clinical Particulars

BNF therapeutic class	Section 2: Piperazine Derivatives
Cautions and Contraindications	**Contra-indications:** Ranolazine is contraindicated in patients with severe renal impairment (CrCl <30 ml/min) and moderate or severe hepatic impairment (Child-Pugh score B-C). Concomitant administration of potent CYP3A4 inhibitors is contraindicated (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:** Caution in prescribing and dose-titration should also be exercised in the following groups: • Elderly • Patients with low weight (≤ 60 kg) • Patients with moderate to severe CHF (NYHA Class III–IV) • Concomitant administration of moderate CYP3A4 inhibitors (see above) • Concomitant administration of P-gp inhibitors • Mild hepatic impairment (Child-Pugh score A) • Mild to moderate renal impairment (creatinine clearance 30–80 ml/min) • Patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval

Adverse Drug Reactions

Undesirable effects in patients receiving Ranolazine are generally mild to moderate in severity and often develop within the first 2 weeks of treatment and if patients present with any factors as mentioned in the **cautions** listed above.
See types of adverse drug reactions expected with Ranolazine in the table below.

Common	Uncommon	Rare
Dizziness Headache Constipation Vomiting Nausea Asthenia	Anorexia, decreased appetite, dehydration anxiety Insomnia, confusional state, hallucination lethargy, syncope, hypoaesthesia, somnolence, tremor, postural dizziness, paresthesia Blurred vision, visual disturbance, diplopia, vertigo, tinnitus Hot flush Hypotension, dyspnoea, cough, epistaxis, abdominal pain, dry mouth, dyspepsia, flatulence, stomach discomfort, fatigue, peripheral oedema	Hyponatremia Disorientation, Amnesia Depressed or loss of consciousness Coordination abnormal Gait disturbance, Peripheral coldness Orthostatic hypotension Pancreatitis Acute renal failure Urinary retention

Monitoring

Renal Function: the initiating Specialist will check the baseline renal function and again at regular intervals during treatment for those patients who are at increased risk of renal impairment (e.g. elderly patients, pre-existing renal impairment, patients taking medications such as ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists, and patients taking medication which may alter renal blood flow). These should be repeated at as clinically indicated within primary care, which might need to be more frequent for patients at increased risk.

For patients with CrCl between 30 and 80mls/min on a stable dose of ranolazine – advise discussion with the patient to ensure they are not experiencing side effects which might warrant a dose reduction, but do not uptitrate the dose any further.

If CrCl falls below 30mls/min, ranolazine is contraindicated – advise stopping treatment and informing the initiating cardiologist.

Hepatic function: the initiating Specialist will check the baseline hepatic function and again at regular intervals if clinically appropriate.

Patients with mildly deranged LFT's may need more cautious dose titration due to the risk of side effects, but if bilirubin <35 and transaminases are <3x the upper limit of normal (ULN) then no further action is required. It may be best to check the Child-Pugh score in patients with more complex hepatic derangement. Further information on how to score this can be found via the following
link.

Interactions	CYP3A4 or P-gp inhibitors: Inhibitors of CYP3A4 increase plasma concentrations (and therefore, dose-related adverse events) of Ranolazine. Combining Ranolazine with potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone) is **contraindicated**. *Diltiazem* (180 to 360 mg once daily) may cause dose-dependent increases in average Ranolazine concentration. Careful dose titration of Ranolazine is recommended in patients treated with diltiazem and other moderately potent CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Down-titration also may be required. *NB Prescribing with macrolide antibiotics – As mentioned above, combination with clarithromycin is contraindicated due to the risk of QT prolongation, and where possible a different class of antibiotic should be used to treat infections. However, where this is clinically difficult, erythromycin has a lower potential for causing QT prolongation in combination with ranolazine but it would be advisable to halve the dose of ranolazine for the duration of the antibiotic course and counsel the patient to report symptoms of palpitations or dizziness. Azithromycin could also be used as would have an even lower potential for interaction, and wouldn't require ranolazine dose adjustment. The medicines information team at BHNFT will be able to advise on alternative antibiotics if necessary.* Ranolazine is a substrate for P-gp. Inhibitors of P-gp (e.g. ciclosporin, verapamil) increase plasma levels of Ranolazine. Verapamil (120 mg three times daily) increases Ranolazine concentrations, therefore, careful dose titration is recommended in patients treated with P-gp inhibitors. Down-titration may also be required. CYP3A4 inducers: Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy. Ranolazine should *not* be used in patients treated with CYP3A4 inducers (e.g. rifampicin (600mg OD), phenytoin, phenobarbital, carbamazepine, St. John's Wort). Initiation of treatment with Ranolazine should be avoided during administration of inducers of CYP3A4. CYP2D6 inhibitors: Inhibitors of this enzyme may increase plasma concentrations of Ranolazine. *Paroxetine* (20 mg once daily) may increase concentrations of Ranolazine (500mg BD), however, no dose adjustment is required. Ranolazine may increase plasma concentrations of certain sensitive CYP3A4 substrates (e.g. simvastatin, lovastatin) and CYP3A4 substrates with a narrow therapeutic range (e.g. ciclosporin, tacrolimus, sirolimus, everolimus). Dose adjustment of these drugs may be required as Ranolazine may increase their plasma concentrations resulting in increased exposure to adverse drug reactions. Careful monitoring of the narrow therapeutic agents is recommended. Lower doses of metoprolol, propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics; may be required due to possible increase in exposure to these drugs. Plasma exposure of *metformin* (1000 mg twice daily) may increase with co-administration of Ranolazine (500 mg and 1000 mg twice daily). There is a theoretical risk that concomitant treatment of Ranolazine with other drugs known to prolong the QTc interval may increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g. imipramine, doxepin, amitriptyline).

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Communication

GP to specialist
If the GP has concerns over the prescribing of Ranolazine, they will contact the specialist as soon as possible.

Contact names and details

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References

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2. BNF 76 (September 2018 – March 2019). Ranolazine Monograph. Page 210.

3. NICE CG126. Stable Angina: Management. July 2011. Last Updated August 2016. Available at: https://www.nice.org.uk/guidance/cg126

Development Process

This guidance has been produced by Anila George and Gillian Turrell following an AMBER reclassification of Ranolazine as AMBER-G by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 8th May 2019.