Prescribing ranolazine as an adjunct for the management of on-going symptoms in patients with chronic stable angina

The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Ranolazine (Ranexa®) is a novel anti-anginal therapy, and its mechanism of action is poorly understood. It is hypothesised that it exerts an anti-anginal effect by inhibition of the late sodium current in cardiac cells, resulting in improved myocardial relaxation, and therefore reduced diastolic stiffness. Ranolazine is listed by NICE as an option for the treatment of chronic stable angina.

Ranolazine is approved for use locally as an option for the management of on-going angina symptoms despite the use of first-line anti-anginal therapies such as beta-blockers or calcium channel blockers. Ranolazine may be particularly useful where the use of other anti-anginal therapies is limited by bradycardia (heart rate < 50 beats per minute) or hypotension (systolic blood pressure < 90mmHg), as it has little effect on heart rate or blood pressure. It may also be useful where first-line anti-anginal therapies are contraindicated or not tolerated.

See also SLCSN algorithm 'Optimising Prescribing in Chronic Stable Angina' at http://www.slcsn.nhs.uk/prescribing.html

Pay careful attention to the contraindications, cautions and drug interactions listed below before initiating therapy.

Contra-indications	Cautions
– Hypersensitivity to the active substance or any of its excipients – note the 750mg tablet contains lactose – Severe renal impairment (creatinine clearance <30ml/min; eGFR<30ml/min) – Pregnancy and breast-feeding – Moderate to severe hepatic impairment – Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazadone) – Concomitant administration of class Ia or class III anti-arrhythmics, except amiodarone (e.g. quinidine, sotalol) – Concomitant administration of CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St Johns Wort)	– Concomitant administration of moderate CYP3A4 inhibitors or P-gp inhibitors – Mild hepatic impairment – Mild to moderate renal impairment (creatinine clearance 30-80ml/min; eGFR 30-60ml/min) – Elderly – Patients with low bodyweight ≤ 60kg – Patients with moderate to severe HF (NYHA class III-IV) – Congenital or family history of QT prolongation, or patients with known acquired QT interval prolongation or patients taking drugs known to prolong QTc interval

See overleaf for details of drug interactions with ranolazine.

Initiation and dose titration:

- **Ranolazine should be initiated at a dose of 375mg twice daily, increasing to 500mg twice daily after two to four weeks therapy.**
- **If episodes of anginal chest pain still occur after two to four weeks therapy, a further dose increase to a maximum dose of 750mg twice daily may be considered.**

Ranolazine tablets must be swallowed whole, and must not be crushed, broken or chewed. They can be taken with or without food.

Monitoring:

Renal function declines with age, and is therefore important to monitor renal function regularly throughout treatment with ranolazine – renal checks should be performed at least annually, but more frequently if clinically indicated

Adverse effects (see BNF and / or SPC for full list of possible adverse effects)

Adverse effects to ranolazine are usually reported within the first two weeks of therapy and are generally mild to moderate in severity. Commonly reported side effects (occurring in between 1 in 10 and 1 in 100 patients) include dizziness and headache, constipation, nausea and vomiting and asthenia.

There is an increased risk of dose-related adverse effects in the elderly, patients of low bodyweight (≤ 60kg) and patients with mild to moderate renal impairment.

Ranolazine may cause dizziness, blurred vision, confusional state and hallucination, which may affect the ability to drive and use machines.

Should a patient experience dose–related adverse effects during treatment, such as dizziness, nausea and vomiting, down-titration of the ranolazine dose to 500mg or 375mg twice daily should be considered. If symptoms persist, ranolazine therapy should be discontinued.

Common Drug interactions (for full list of interacting drugs see BNF / SPC)	
Interacting Drug	**Mechanism of action/Significance and Action to be taken**
Potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone). Grapefruit juice.	Concomitant use contraindicated. Significantly increases plasma levels of ranolazine leading to increased risk of adverse effects.
Antiarrhythmics: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. dofetilide, sotalol) other than amiodarone.	
Concomitant treatment with moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, erythromycin) and P-glycoprotein (P-gp) inhibitors (e.g. verapamil, ciclosporin)	Careful dose titration is recommended. Increased plasma levels of ranolazine leading to increased risk of dose related side effects.
CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's Wort)	Concomitant use contraindicated. Co-administration with CYP3A4 inducers is expected to lead to lack of efficacy.
CYP3A4 substrates with a narrow therapeutic range (e.g. ciclosporin, tacrolimus, sirolimus, everolimus).	Concomitant administration of ranolazine may increase plasma levels - dose adjustment of these drugs may be necessary. Monitor plasma levels carefully.
Metoprolol or other CYP2D6 substrates (e.g. propafenone and flecainide or, to a lesser extent, tricyclic antidepressants and antipsychotics).	Concomitant administration of ranolazine may increase plasma levels of these drugs. Dose reduction may be necessary.
Co-administration with CYP2B6 substrates (e.g. bupropion, efavirenz, cyclophosphamide).	Caution advised – concomitant administration has not been evaluated.
Digoxin	Increased digoxin levels. Monitor digoxin levels at initiation, throughout therapy and on cessation of ranolazine therapy
Simvastatin	Maximum dose of simvastatin 20mg daily – or consider alternative statin. Rhabdomyolysis has been seen with higher doses of simvastatin.
Drugs known to prolong the QTc interval including certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, and tricyclic antidepressants (e.g. imipramine, doxepin, amitriptyline)	Theoretical risk that concomitant treatment with ranolazine may increase the possible risk of ventricular arrhythmias

As a black triangle drug for this indication all adverse effects should be reported to the CSM using the yellow card system, even if well documented, in addition to any local reporting arrangements

References

1. *Summary of Product Characteristics, Ranexa. Amended 24.04.2012. Accessed at: http://www.medicines.org.uk/emc/medicine/21402/SPC/Ranexa+prolonged-release+tablets/*
2. *NICE CG126 guidance. Management of chronic stable angina 2011*