Coventry & Warwickshire

Area Prescribing Committee

Drug Positioning Statement — DPS009

Dronedarone (Multaq®) — October 2013

VERDICT

The Coventry & Warwickshire APC recommends that dronedarone should be initiated by a specialist and, after the patient is stabilised on treatment, prescribing may be continued in primary care under shared care arrangements. When requests for ongoing treatment in primary care are made this should be accompanied by the relevant shared care agreement.

Specialist Drugs List Status: Shared Care (SC)

Summary notes[1]

Indication:

Indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistant atrial fibrillation. Dronedarone should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

Due to its safety profile, dronedarone should only be prescribed after alternative treatment options have been considered.

Pharmacological action: **Dronedarone** is a multichannel blocking, anti-arrhythmic benzofuran derivative

Presentation : Available as 400mg tablets

Dose: 400mg twice daily with morning and evening meals *(not to be taken with grapefruit juice).* **Treatment should be initiated and monitored only under specialist supervision**

Cost comparison (30 days supply)[2]:

Dronedarone 400mg bd	£67.50
Amiodarone 200mg daily	£1.90
Sotalol 80mg to 320mg twice daily	£3.26-£20.88
Propafenone 300mg twice to three times daily	£17.43-£26.15
Flecainide 50mg to 150mg twice daily	£3.95-£10.08

Drug profile

Clinical Effectiveness

There are 7 efficacy trials. In a systematic review and indirect comparison meta-analysis [3,4,5] of amiodarone (4 studies) and dronedarone (4 studies), amiodarone but not dronedarone, significantly reduced the risk of recurrent AF vs. placebo. In contrast, there was also a trend toward greater all-cause mortality and greater overall adverse effects requiring drug discontinuation with amiodarone vs. dronedarone.

- **The ATHENA study (n=4628)** focused on morbidity and mortality. Dronedarone was shown to reduce the risk of CV hospitalisations or all cause death by a statistically significant 24%. The absolute risk reduction 7.5% and NNT =13 for CV hospitalisation or all cause mortality at 1 year.
- **DIONYSIS**, a 6 month active comparator trial (n=504) with amiodarone is yet to be fully published. However results of DIONYSIS are consistent with other studies and show dronedarone to be less effective than amiodarone.

The PALLAS study[6] (Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy) had been investigating the potential clinical benefit of dronedarone (added to standard therapy) in patients older than 65 years with permanent atrial fibrillation in the reduction of major cardiovascular (CV) events (ie, stroke, systemic arterial embolism, myocardial infarction, or cardiovascular death or unplanned cardiovascular hospitalisation or death from any cause The study was prematurely terminated in July 2011, when an interim analysis showed a significant excess of CV-related deaths, stroke, and hospitalisations due to CV events in the dronedarone group compared with placebo.

Safety

Dronedarone is associated with fewer side effects leading to discontinuation compared with amiodarone; the most common adverse events are diarrhoea, nausea, bradycardia, abdominal pain, vomiting, rash and asthenia. No excess thyroid or pulmonary toxicity, photosensitivity or pro-arrhythmic events have been identified in the published clinical trials.

Dronedarone is contra-indicated in severe hepatic or renal impairment. An initial elevation in plasma creatinine levels 7 days after initiation is expected and does not represent reduced renal function [1,7]. If this plateaus, this should be used as the new baseline.

As a result of concerns over reports of liver injury, including two cases of liver failure requiring transplantation, the SPC now recommends monthly liver-function testing for the first 6 months of treatment, and at 9 and 12 months after treatment initiation. The review was extended to include cardiovascular and pulmonary safety after the premature termination of the PALLAS study and several reported cases of pulmonary injury which may have been associated with dronedarone . CHMP guidance[8] concluded that the benefits of treatment continue to outweigh the risks for the maintenance of sinus rhythm after successful cardioversion in a limited population of patients with paroxysmal or persistent atrial fibrillation; however, in light of safety concerns dronedarone should only be prescribed after other treatment options have been considered. Regular monitoring of cardiac, liver, renal and pulmonary function during treatment is recommended.

Drug profile (Continued)

Dronedarone is also contra-indicated in patients[1] with second- or third- degree Atrio-Ventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker); history of, or current heart failure or left ventricular systolic dysfunction,permanent AF with an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician; bradycardia< 50bpm; concomitant use of potent CYP3A4 inhibitor; drugs/herbal products that prolong QT interval and QT Bazett interval>500ms.

Dronedarone also significantly interacts with digoxin and simvastatin[1]

Current place in therapy

National institute for Health and Clinical Excellence (NICE)

NICE[9] has issued guidance on the use of dronedarone for treatment of non-permanent AF. The guidance restricts the use of dronedarone as a 2nd line option for the treatment of non-permanent AF only in people whose AF is not controlled by first line therapy (usually includes b-blockers) and who have at least one specific cardiovascular risk factor (hypertension, diabetes, previous TIA, stroke or systemic embolism left atrial diameter of 50mm or greater, LVEF less than 40%, aged 70 years or older) **and who do not have** unstable NYHA class lll or lV heart failure.

Scottish Medicines Consortium (SMC)[10]

Accepted for restricted use within NHS Scotland. Restriction : for the prevention of recurrence of AF in patients in whom beta blockers, class 1c drugs or amiodarone are contra-indicated, ineffective or not tolerated. Treatment should be initiated on specialist advice only. Dronedarone appears less effective than amiodarone in reducing atrial fibrillation recurrence but has the potential for improved tolerability compared to comparator medicines

Midlands Therapeutics Review and Advisory Committee (MTRAC)[11]

Suitable for prescribing under defined conditions. The strength of evidence for efficacy was rated as moderately strong. Three RCTs showed that dronedarone was no more effective than placebo in preventing recurrence of atrial fibrillation but had no effect on the secondary outcome of all cause mortality; other secondary outcomes showed lower cardiovascular related mortality with dronedarone. In a fourth RCT, it was less effective at preventing recurrence of AF than amiodarone. As a result, and the lack of long term safety data gives it a lower place in therapy.
The commissioning guidance also states that Dronedarone should be initiated in secondary care to ensure that patients with structurally abnormal hearts are excluded and because of the need to try other treatments first. Patients can be transferred to primary care for continued prescribing of dronedarone when appropriate, with the guidance of an ESCA. Liver function monitoring should be carried out as recommended by the Summary of Product Characteristics and the MHRA guidance.

Summary

Whilst dronedarone is less effective in maintaining sinus rhythm in patients with a history of AF than amiodarone, and is more expensive, short-term evidence suggests **that it is associated with fewer side-effects leading to discontinuation compared to amiodarone** and does not require specialist dosage titration.

Following a review of the safety of dronedarone, the Commission on Human medicines (CHMP) now recommend that dronedarone should be used only for the maintenance of sinus rhythm after successful cardioversion in patients with paroxysmal or persistent atrial fibrillation (AF). Because of safety concerns, dronedarone should only be prescribed after alternative treatment options have been considered.
Dronedarone should not be given to patients with left ventricular systolic dysfunction, or to patients with current or previous episodes of heart failure.
CHMP considered that treatment with dronedarone should be initiated and monitored only under specialist supervision. Further contraindications for use and cardiac, pulmonary, renal and hepatic recommendations for monitoring were also endorsed by the CHMP.

References

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5. J Am Coll Cardiol, 2009; **54** : 1089-1095
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11. MTRAC. Dronedarone commissioning guidance. For the treatment of non permanent atrial fibrillation. March 2010