

# NEW DRUG EVALUATION

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## DRONEDARONE

Dronedarone is an oral anti-arrhythmic drug (AAD), indicated for clinically stable patients with a history of non-permanent atrial fibrillation (AF), for preventing recurrence of AF, or reducing ventricular rate (VR). In randomised trials dronedarone appears to be more effective than placebo at reducing AF recurrence, but less effective than amiodarone. Short-term data however, suggests that dronedarone is likely to result in fewer adverse effects than amiodarone, and unlike other AADs dose not appear to be associated with an increased risk of mortality. In line with preliminary NICE guidance, dronedarone is recommended as a second-line treatment option for AF only in those patients with additional cardiovascular risk factors.

### What is it?

Dronedarone (Multaq<sup>®</sup>, Sanofi-Aventis) is an oral Class III anti-arrhythmic drug licensed for use in clinically stable adult patients with non-permanent atrial fibrillation (AF), for preventing recurrence of AF or reducing ventricular rate (VR).<sup>1</sup> Dronedarone is similar in structure and function to amiodarone, an established anti-arrhythmic drug that is available generically with low acquisition costs. Unlike amiodarone however, dronedarone does not contain iodine; thyroid dysfunction is reported in up to 10% of patients receiving long-term amiodarone treatment, but monitoring of thyroid function is not required for dronedarone.<sup>2</sup>

Treatment with dronedarone may be initiated in an outpatient setting, at a recommended dose of 400 mg twice daily with food.<sup>1</sup>

### How effective is it?

The efficacy of dronedarone in maintaining sinus rhythm and in controlling VR during recurrences of AF has been compared with placebo in two identical double-blind, randomised, controlled trials (EURIDIS & ADONIS).<sup>3</sup> Patients with a history of AF or atrial flutter (AFL) were randomised to receive dronedarone 400 mg twice daily (n = 828) or placebo (n = 409). For the two trials combined, the median time from randomisation to the first documented recurrence of AF (primary endpoint) was 116 days in the dronedarone group vs. 53 days with placebo. After 12 months of treatment, the rates of AF recurrence were 64.1% vs. 75.2% respectively (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.65 to 0.87; p<0.001).<sup>3</sup> The mean VR during AF recurrence was lower in the dronedarone arm in both trials (p<0.001).<sup>3</sup> A post-hoc analysis showed that 22.8% of patients receiving dronedarone had either been hospitalised or died at 12 months, compared to 30.9% of those in the placebo arm (HR, 0.73; CI, 0.57 to 0.93, p=0.01). The rates of sudden death and death from any cause did not differ significantly between the two groups.<sup>3</sup>

The large (n = 4,628) randomised, double-blind, placebo-controlled ATHENA trial, assessed the efficacy of dronedarone

on cardiovascular (CV) events in patients with AF.<sup>4</sup> The study population was a moderate to high risk, elderly population, which differs from other trials. Patients received dronedarone 400 mg twice daily or placebo, with a minimum of 12 months follow-up. Comparing dronedarone and placebo recipients, 743 (31.9%) vs. 917 (39.4%) had a primary outcome of hospitalisation due to CV events or death from any cause (HR, 0.76; CI, 0.69 to 0.84 p<0.001), 675 (29.3%) vs. 859 (36.9%) were hospitalised due to CV events (p<0.001), and 59 (2.6%) vs. 58 (2.5%) died before hospitalisation.<sup>4</sup>

DIONYSOS is the only trial which directly compares the efficacy of dronedarone to that of another anti-arrhythmic drug. The trial is currently unpublished and data were provided by the manufacturer.<sup>5</sup> This six-month, randomised, double-blind study compared the efficacy and safety of dronedarone (400 mg twice daily n = 249) and amiodarone (600 mg daily for 28 days, 200 mg daily thereafter, n = 255) in patients with AF. The primary efficacy endpoint was treatment failure, defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. In the dronedarone group 73.9% of patients reached the primary endpoint, compared to 55.3% of those in the amiodarone arm (HR, 1.59; CI, 1.28 to 1.98 p<0.001).<sup>5</sup> Premature drug discontinuation due to adverse events was more common in the amiodarone arm than the dronedarone arm (34/255 vs. 26/249).

### How safe is it?

A phase III, randomised, controlled trial in patients hospitalised with symptomatic heart failure and severe left ventricular systolic dysfunction (ANDROMEDA) was terminated early because of an increased risk of death due to worsening heart failure with dronedarone compared to placebo.<sup>6</sup> During the study period, 25 patients (8.1%) receiving dronedarone died, compared to 12 (3.8%) in the placebo group (HR 2.13, 95% CI, 1.07 to 4.25). Caution must be exercised when extrapolating these data to the licensed AF indication because the study population had a high mortality risk prior to treatment with dronedarone. Because of these results, the use of dronedarone in unstable patients with New York Heart Association (NYHA) class III and IV heart failure is contraindicated.<sup>1</sup>

The adverse events (AEs) profile for dronedarone suggests it is well tolerated, with the most common AEs being: diarrhoea, nausea, vomiting and abdominal pain.<sup>3,4</sup> In the EURIDIS/ADONIS trials elevated serum creatinine (2.4% vs. 0.2%, p=0.004) and hyperthyroidism (8.4% vs. 14.1%, p=0.002) were more common with dronedarone than with placebo.<sup>3</sup> In the ATHENA trial, AEs which occurred more frequently with dronedarone treatment than placebo included: bradycardia, QT interval prolongation, diarrhoea, nausea, rash and serum creatinine elevation.<sup>4</sup>

Preliminary data from the short-term DIONYSOS study suggests that dronedarone has a more favourable safety profile than amiodarone.<sup>5</sup> There is no direct evidence comparing the adverse effects of dronedarone with other AADs.

All suspected adverse reactions to black triangle drugs such as dronedarone should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

NICE clinical guideline 36 sets out clear pathways for the management of different presentations of AF.<sup>7</sup> Standard beta-blockers are suitable for both rate and rhythm-control

strategies and are recommended for first-line use in the majority of situations. Rate-limiting calcium antagonist and digoxin are alternatives for rate control. Sotalol and class 1c agents, such as flecainide and propafenone, are alternatives for rhythm control. Amiodarone is reserved for specialist use when other AADs have been tried.<sup>7</sup>

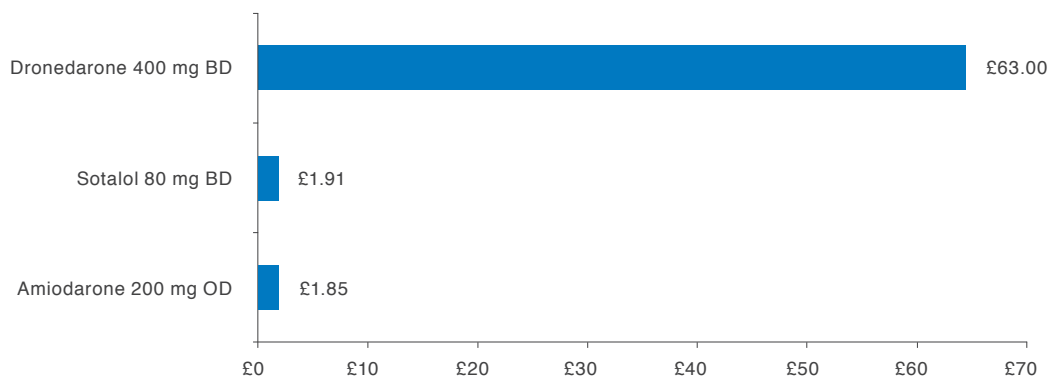
### When should it be used?

Dronedarone should only be used as a treatment option in those patients with additional cardiovascular risk factors whose AF is not adequately controlled by first-line therapy. Dronedarone appears to be more effective than placebo at reducing AF recurrence,<sup>3,4</sup> but is less effective than amiodarone.<sup>5</sup> Short-term data however, suggests that dronedarone is likely to result in fewer adverse effects than amiodarone, and unlike other AADs dose not appear to be associated with an increased risk of mortality.<sup>5</sup> Longer-term comparative data are necessary to fully establish the efficacy and safety of dronedarone relative to other AADs.

NICE has published preliminary guidance recommending dronedarone as a second-line treatment option for AF only in those patients with additional cardiovascular risk factors. Full guidance is expected to be published in June 2010.<sup>8</sup>

### How much does it cost?

Cost of 28 days treatment (Drug Tariff & eMIMS, March 2010)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. Average daily quantity (ADQ) values are used where available.

## REFERENCES

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KEY: R - review, RCT - randomised controlled trial, G - guideline

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