Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

dronedarone, 400mg, film-coated tablets (Multaq®) SMC No. (636/10)

Sanofi-aventis Ltd

6 August 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

dronedarone (Multaq®) is accepted for restricted use within NHS Scotland.

Indication under review: in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

SMC 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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Dronedarone is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Dosing Information

400mg twice daily, with morning and evening meals.

Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting dronedarone.

Product availability date

30 March 2010

Summary of evidence on comparative efficacy

Atrial fibrillation (AF) is the most frequent sustained arrhythmia. It is associated with an increased risk of cardiovascular events including stroke, greater all-cause mortality and has a detrimental impact on quality of life. Dronedarone is an anti-arrhythmic agent in the benzofurane class, which includes amiodarone. It demonstrates electrophysiological characteristics belonging to all four Vaughan-Williams classes of anti-arrhythmic compounds.

Evidence to support this indication was from three phase III, randomised, double-blind, placebo-controlled studies. Two were identical in design, being conducted in Europe and the rest of the world, and demonstrated the 1-year efficacy of dronedarone in the maintenance of normal sinus rhythm after conversion of AF or atrial flutter (AFL), while the other evaluated dronedarone in patients with AF who had additional risk factors for death, for a minimum of 12 months. There was a fourth active-comparator, 6-month study comparing the efficacy and safety of dronedarone with amiodarone, in patients with persistent AF.

In the two, 12-month identical placebo controlled studies (n=612 and n=625), patients over 21 with at least one episode of AF recorded on an electrocardiogram (ECG) in the preceding 3 months were included if they were in sinus rhythm for at least one hour before randomisation. Those with permanent AF or New York Heart Association (NYHA) class III or IV congestive heart failure were excluded. Patients were randomised 2:1 to receive either dronedarone or placebo in addition to baseline therapy. Patients were followed up with a clinical evaluation and regular ECG monitoring for a minimum of 12 months. The primary end point was the time from randomisation to the first documented recurrence of atrial fibrillation, defined as an episode lasting for at least 10 minutes and confirmed by two consecutive ECG recordings taken 10 minutes apart, in a modified intention to treat (ITT) population.

Combining the results from the two studies, 828 patients were randomised to receive dronedarone 400mg twice daily and 409 to placebo. The mean age was 63 years, 69% were male, between 55 and 58% of patients were receiving beta-blockers and approximately 70% received oral anticoagulation. The median time to a documented recurrence of AF was 116 days in the dronedarone group and 53 days in the placebo group.

By 12 months, the rate of recurrence was 64% in the dronedarone group and 75% in the placebo group (hazard ratio [HR] 0.75; 95% confidence interval [CI]: 0.65 to 0.87).

The third placebo controlled study included patients with paroxysmal or persistent AF or AFL. Patients were required to have at least one additional risk factor. This criteria was met if patients were aged ≥ 70 years and had no additional risk factors or if patients were less than 70 years old and had hypertension, diabetes, prior cerebrovascular accident, left atrial diameter greater ≥ 50mm or left ventricular ejection fraction ≤40%. Patients could be enrolled while in sinus rhythm (if conversion had occurred) or in AF/AFL, but required an ECG within the previous 6 months documenting that they had been in AF/AFL and another documenting sinus rhythm in this period. During the course of the study, overall mortality figures were lower than expected, so the protocol was amended. Patients younger than 70 years old were no longer eligible, patients ≥ 75 years were eligible regardless of pre-existing risk factors and patients aged between 70 and 74 years were required to have one or more additional risk factors. Patients were randomised, in a 1:1 ratio, to receive dronedarone or placebo. Randomisation was stratified by centre and by the presence or absence of AF/AFL at randomisation. Treatment was in addition to baseline therapy. Patients were followed up with a clinical evaluation regularly, for a minimum of 12 months. The primary composite end-point was the first unplanned hospitalisation due to cardiovascular events, or death from any cause, in the ITT population.

The study recruited 4,628 patients, of whom 2,301 were randomised to dronedarone 400mg twice daily and 2,327 to placebo. Overall, the mean age was 72 years, 47% were female and baseline therapy included 70% of patients on beta-blockers (excluding sotalol) and 60% on anticoagulation. At randomisation, 25% had AF, 86% had hypertension, 60% had structural heart disease and 4% had class III NYHA heart failure. Follow-up was for a mean of 21 months. In patients randomised to dronedarone, 734 (32%) had a primary outcome event, including 675 patients (29%) with a hospitalisation due to cardiovascular events and 116 (5%) who died. In the placebo group, 917 (39%) had a primary outcome event, including 859 (37%) with a hospitalisation due to cardiovascular events and 139 (6%) who died. The HR for the primary outcome in the dronedarone group was 0.76 (95% CI: 0.69 to 0.84).

The active-comparator study recruited patients aged 21 years or older with documented AF for more than 72 hours, for whom cardioversion and anti-arrhythmic treatment were indicated and who were receiving oral anticoagulants. Patients with paroxysmal AF, AFL, severe congestive heart failure ((NYHA) class III or IV) were excluded. Patients were randomised to dronedarone 400 mg twice daily (n=249) or amiodarone 600 mg daily for 28 days then 200 mg daily (n=255) thereafter, for at least 6 months. The duration of follow-up was 6 months after the last patient was included and included scheduled and unscheduled ECGs. The primary efficacy endpoint was defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy.

Mean age was 64 years, with 20% of patients aged 75 years or older. One-third of patients were female and 63% had a history of persistent AF. The incidence of the composite primary efficacy end-point at 12 months was 75% in the dronedarone group and 59% in the amiodarone group (HR 1.59; 95% CI: 1.28 to 1.98). The crude rates for the composite primary endpoint and its components show that it was mainly driven by the AF recurrence component (including absence of conversion), which was more frequent in the dronedarone group (64%) compared with the amiodarone group (42%). Driven mainly by intolerance, the premature drug discontinuation component was less frequent in the dronedarone group (10% versus 13%, respectively).

Summary of evidence on comparative safety

In the two pooled placebo-controlled studies, dronedarone had a higher rate of diarrhoea (7.1% versus 4.9%), nausea (4.3% versus 3.4%) hypothyroidism (5.5% versus 3.5%) and elevated serum creatinine (2.4% versus 0.2%). Cardiac events were also more frequent. The placebo group fared worse for hyperthyroidism (14.1% versus 8.4%) and liver abnormalities (13.6% versus 12.2%). No episodes of torsades de pointes were reported.

The placebo-controlled study in 4,628 patients reported treatment-emergent adverse events in 72% of the dronedarone patients and 69.3% of the placebo group. Gastrointestinal events (26% versus 22%), skin-related events (10% versus 7.6%) and cardiac events (11% versus 9.6%) were more common in the dronedarone group, with respiratory and neurological events being of a similar magnitude to the placebo group (14% and 16% for each type of event). Again there was a significant increase in serum creatinine in the dronedarone group (4.7% versus 1.3%). There was one case of torsades de pointes.

In the active-comparator study, a main safety endpoint (MSE) measured the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal (GI) events, or premature study drug discontinuation following an adverse event. The incidence of the MSE was 39% and 44% in the dronedarone and amiodarone groups, respectively, at 12 months' treatment. This was mainly driven by fewer thyroid, neurological, skin, and eye events. More GI events, mainly diarrhoea, were observed in the dronedarone group, none of which were serious. No pulmonary-specific events were reported in either treatment group. A pre-specified analysis of the MSE excluding GI events found a significantly lower incidence of clinically severe adverse events with dronedarone (HR 0.61; 95% CI 0.44 – 0.84).

The rate of premature treatment discontinuation was higher with dronedarone than with amiodarone (39% versus 27%). Discontinuation due to lack of efficacy was greater with dronedarone (21% versus 5.5%) and discontinuation due to adverse events was greater with amiodarone (13% versus 18%).

The incidence of serious treatment-emergent adverse events was similar in both groups (13.7% versus 14.5% for dronedarone and amiodarone, respectively). Among these, cardiac disorders were reported in 4.4% of dronedarone-treated patients and 6.3% of amiodarone-treated patients.

Both treatment groups saw a similar increase in creatinine plasma levels. Mean changes from baseline in digoxin levels were similar in both treatment groups. Analysis of the INR data showed a higher proportion of patients with supratherapeutic INR levels (above 4.5) in the amiodarone group throughout the study, compared with dronedarone. Abnormal levels of thyroid function parameters were more frequent in the amiodarone group.

Summary of clinical effectiveness issues

The presented data demonstrate the efficacy of dronedarone as an anti-arrhythmic in patients in AF, in terms of rhythm control. It has been shown to decrease the risk of AF-related hospitalisations, in an elderly, moderate-high risk population.

In one comparative study, dronedarone appeared less effective than amiodarone in the maintenance of sinus rhythm, but it was associated with a significantly reduced rate of severe adverse events.

The largest, placebo-controlled study which analysed hospitalisations and mortality outcomes was conducted in an older, moderate to high risk population. The study population appears broadly representative of the Scottish population of AF patients. Post-hoc analysis showed the effect to be consistent across various risk sub-groups. Results from this study were supported by post-hoc analysis from the two smaller studies where the patients were younger and lower risk.

A range of meta-analyses were presented in order to compare dronedarone to other available anti-arrhythmic therapies, including amiodarone, sotalol and class 1c drugs. The earlier analyses suffered from being carried out before all data were available. A mixed treatment comparison (MTC) analysis had potential bias due to the exclusion of studies with zero events in a treatment arm. Despite the evidence from the two smaller placebo-controlled studies showing dronedarone to be effective at reducing AF recurrence, the results from the MTC showed that dronedarone is not as effective as amiodarone, sotalol or class 1c agents. The MTC suggested, however, that the risk of death with dronedarone relative to the other anti-arrhythmics is significantly lower.

From the mixed treatment comparison analyses provided, dronedarone performed less well than comparators on clinical end-points (AF recurrence) but performed at least as well as other anti-arrhythmics on outcome end-points (all-cause mortality).

Although in the same pharmacological class as amiodarone, dronedarone is structurally different and does not contain iodine, the component that is associated with pulmonary and thyrotoxic effects. A key weakness of the data on dronedarone provided is that the studies were not long enough to establish the risks of all potential adverse events, particularly those with a long latency such as pulmonary toxicity. In addition, none of the studies captured any quality of life data.

Dronedarone is contraindicated in patients with NYHA class III and IV heart failure.

SMC clinical experts have indicated that the side-effect profile of amiodarone is problematic and that there is an unmet need for a better tolerated alternative, particularly in younger patients. The data provided suggest that dronedarone may have a more favourable adverse effect profile than amiodarone.

Summary of comparative health economic evidence

The manufacturer presented a complex lifetime cost-utility analysis based on a discrete event simulation to estimate the effects of dronedarone relative to either amiodarone, sotalol or class 1c drugs (propafenone and flecainide) in patients with either paroxysmal or persistent AF. These comparators were appropriate, but given the clinical effectiveness estimates it would also have been appropriate to have considered an additional comparator of no active treatment.

Modelling saw those patients moving into permanent AF continue with their current treatment, apparently implying that dronedarone patients continued with use of dronedarone. This may have been to the benefit of dronedarone.

For the comparison with amiodarone and sotalol, a mixed treatment comparison provided estimates suggesting that dronedarone performed less well for the licensed indication of prevention of AF recurrence, but was better for all-cause mortality, stroke prevention and discontinuation rates.

For the comparison with the class 1c drugs, the mixed treatment comparison provided estimates suggesting that dronedarone performed less well for the prevention of AF recurrence and marginally less well for discontinuation rates. No evidence was found in the mixed treatment comparison for all-cause mortality and stroke prevention. As a consequence, the manufacturer assumed dronedarone and the class 1c drugs were equivalent for all-cause mortality. For the risk of stroke, the superiority estimated for dronedarone over placebo in the mixed treatment comparison was assumed to cross over to superiority for dronedarone over the class 1c drugs.

The mixed treatment comparison was augmented by an informal comparison of adverse event rates. This mainly affected the comparison with the class 1c drugs. It was a principal reason the manufacturer estimated an acceptable cost-effectiveness ratio for dronedarone compared to the class 1c drugs.

Risk equations for times to events were drawn from the placebo arm of the pivotal dronedarone trial, with the odds ratios for the active treatments being applied to these. All cause mortality was augmented with a relative risk determined by the patient's $CHADS_2$ score. Additional mortality risks were added associated with stroke and CHF.

Utilities were taken from a large twelve month EQ-5D European study, though the manufacturer re-estimated the equations within this restricting the analysis to only those outcomes modelled within the economics. The direct drug costs were augmented by initiation and monitoring costs, these latter tending to reduce the net direct drug cost. Other resource use was mainly drawn from the literature.

The manufacturer presented the following results from the model:

- An incremental cost per quality adjusted life year (QALY) of £2,406 for dronedarone compared to amiodarone based on additional costs of £4,304 and 1.79 additional QALYs;
- An incremental cost per QALY of £1,911 for dronedarone compared to sotalol, based on additional costs of £4,167and 2.18 extra QALYs;
- An incremental cost per QALY of £18,737 for dronedarone compared to class 1c drugs based on additional costs of £2,380 and 0.13 extra QALYs.

Weaknesses of the analysis included:

- the mixed treatment comparison excluded studies with zero events in a treatment arm but provision of additional analysis which included these studies indicated that the cost-effectiveness ratios were still acceptable;
- the inputs to the modelling of dronedarone compared to the class 1cs were largely by assumption, but relatively conservative assumptions were used;
- possible double counting within monitoring costs given that patients are likely to have frequent GP contacts. Additional analysis indicated, however, that this was not an important driver of the results;
- cost offsets from adverse events not being adequately justified within the submission, particularly for class 1c drugs, but again sensitivity analysis to address this issue showed that the results still remained acceptable.

In summary, there were a number of limitations with the analysis but the cost-effectiveness ratio remained acceptable in the various sensitivity analyses that were presented to address the concerns.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- The Stroke Association
- Atrial Fibrillation Association

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 94 "Cardiac arrhythmias in coronary heart disease" in February 2007. The guideline predates dronedarone and recommends that amiodarone or sotalol treatment should be considered where prevention of atrial fibrillation recurrence is required on symptomatic grounds.

The National Institute for Health and Clinical Excellence (NICE) published a clinical guideline (number 36) entitled "Atrial fibrillation: National clinical guideline for management of atrial fibrillation in primary and secondary care" in June 2006. The guideline predates dronedarone. The recommendation for patients with persistent AF who require anti-arrhythmic drugs is for a standard beta-blocker. Where this is inappropriate, for those with structural heart disease, amiodarone is the next option; if there is no structural disease, a Class 1c agent or sotalol is recommended, followed by amiodarone. For patients with paroxysmal AF, the recommendation is for a standard beta-blocker. Where this is inappropriate, if there is no structural disease, the recommendation is to use a Class 1c drug or sotalol, then amiodarone. If there is coronary artery disease, then sotalol is recommended, followed by amiodarone, and if there is poor left ventricular function, then the next option is amiodarone.

In 2006, there was a joint publication from the American Heart Association / American College of Cardiology / European Society of Cardiology entitled "Guidelines for the managements of patients with atrial fibrillation". Again these were published before the availability of dronedarone. The treatment of persistent and paroxysmal AF is essentially the same and involves a Class 1c drug or sotalol if there is no structural disease, with amiodarone as the next option. For those with heart failure or left ventricular hypertrophy, amiodarone is recommended; sotalol is recommended for those with coronary artery disease, followed by amiodarone, and if there is hypertension, then a Class 1c drug is recommended, followed by amiodarone or sotalol.

Additional information: comparators

Anti-arrhythmic agents amiodarone, sotalol, flecainide and propafenone.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
dronedarone	**400mg twice daily, orally**	**819**
amiodarone	200mg daily, orally	37
sotalol	80mg to 320mg twice daily, orally	25 to 124
propafenone	300mg twice to three times daily, orally	113 to 170
flecainide	50mg to 150mg twice daily, orally	88 to 224

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 9 June 2010.

Additional information: budget impact

The manufacturer presented budget impact estimates that included direct drug costs and also downstream resource costs and savings associated with adverse events and monitoring. This resulted in a net budget impact of £877k in year one rising to £2.67m in year five. These estimates were based on patient numbers of 2,390 in year one and 7,291 in year five, given an eligible patient population of between around 12,000 and 14,000 and market share projections of 20% in year one and 50% in year five.

The manufacturer did not present drug budget only estimates but did state that dronedarone would cost £821 per patient per year compared to an average of £56 per patient per year for the comparator treatments. Given these figures, this would imply a gross drug cost of £1.96m in year 1, rising to £5.98m by year 5 and a net drug budget impact of £1.8m in year 1, rising to £5.6m by year 5.

The budget impact estimates provided by the manufacturer did not take into account the SMC restriction in the eligible patient population.

References

The undernoted references were supplied with the submission.

Singh BN, Connolly SJ, Crijns HJ et al and EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Eng J Med. 2007; 357: 987-99.

Hohnloser SH, Crijns HJ van Eickels M et al and ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Eng J Med. 2009; 360: 668-78.

Le Heuzey J-Y, de Ferrari GM, Radzik D et al. A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study. J Cardiovasc Electrophysiol, 2010; 1-9.

European Medicines Agency. Assessment Report for Multaq. EMEA/H/C/001043. 2009 http://www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 16 July 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.