

Issue date: August 2010

Dronedarone for the treatment of non-permanent atrial fibrillation

**This guidance was developed using the
single technology appraisal process**

NICE technology appraisal guidance 197

Dronedarone for the treatment of non-permanent atrial fibrillation

Ordering information

You can download the following documents from www.nice.org.uk/guidance/TA197

- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- ‘Understanding NICE guidance’ – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or ‘Understanding NICE guidance’, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2274 (quick reference guide)
- N2275 (‘Understanding NICE guidance’).

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, 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.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London WC1V 6NA

www.nice.org.uk

© National Institute for Health and Clinical Excellence, 2010. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the express written permission of NICE.

Contents

1	Guidance	4
2	The technology	4
3	The manufacturer's submission	5
4	Consideration of the evidence	21
5	Implementation	33
6	Recommendations for further research	33
7	Related NICE guidance	33
8	Review of guidance	34
	Appendix A: Appraisal Committee members and NICE project team	35
	Appendix B: Sources of evidence considered by the Committee	39



NHS Evidence has accredited the process used by the Centre for Health Technology Evaluation at NICE to produce guidance. Accreditation is valid for 3 years from April 2010 and is applicable to guidance produced using the processes described in NICE's 'Guide to the single technology appraisal process' (2009). More information on accreditation can be viewed at www.evidence.nhs.uk

1 Guidance

1.1 Dronedarone is recommended as an option for the treatment of non-permanent atrial fibrillation **only** in people:

- whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option, **and**
- who have at least one of the following cardiovascular risk factors:
 - hypertension requiring drugs of at least two different classes
 - diabetes mellitus
 - previous transient ischaemic attack, stroke or systemic embolism
 - left atrial diameter of 50 mm or greater
 - left ventricular ejection fraction less than 40% (noting that the summary of product characteristics [SPC] does not recommend dronedarone for people with left ventricular ejection fraction less than 35% because of limited experience of using it in this group) **or**
 - age 70 years or older, **and**
- who do not have unstable New York Heart Association (NYHA) class III or IV heart failure.

1.2 People who do not meet the criteria in section 1.1 who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Dronedarone (Multaq, Sanofi-Aventis) is an antiarrhythmic drug belonging to the benzofuran class of antiarrhythmic compounds. Dronedarone has a marketing authorisation for the treatment of adult clinically stable patients with a history of, or current,

non-permanent atrial fibrillation to prevent recurrence of atrial fibrillation or to lower ventricular rate.

- 2.2 The SPC states that because of the unexplained results of the ANDROMEDA study, the use of dronedarone in unstable patients with NYHA class III and IV heart failure is contraindicated. There is also a recommendation in the SPC (under 'special warnings and precautions for use') which states that because of limited experience in stable patients with recent (1 to 3 months) NYHA class III heart failure or with left ventricular ejection fraction less than 35%, the use of dronedarone is not recommended in these patients.
- 2.3 According to the SPC, the most frequently observed adverse events in people receiving dronedarone are elevated blood creatinine levels and prolongation of the QT interval. Other common adverse events include bradycardia, gastrointestinal events such as diarrhoea and vomiting, rashes, pruritus, fatigue and asthenia. For full details of side effects and contraindications, see the SPC.
- 2.4 The recommended dosage of dronedarone is 400 mg twice daily. Dronedarone is available in 400 mg tablets and comes in packs of 20 tablets or 60 tablets. The cost of a pack of 20 tablets is £22.50 and the cost of a pack of 60 tablets is £67.50 (excluding VAT; 'Monthly index of medical specialities' [MIMS]). The cost per patient per day based on the recommended dosage is £2.25 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of dronedarone and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer's submission presented the use of dronedarone in two positions in the rhythm control treatment pathway for paroxysmal and persistent atrial fibrillation. According to 'The management of atrial fibrillation' (NICE clinical guideline 36), beta-blockers (in addition to anticoagulation) should be the initial treatment option for people with symptomatic paroxysmal atrial fibrillation and people with persistent atrial fibrillation in whom an antiarrhythmic drug is needed to maintain sinus rhythm after cardioversion. For those in whom standard beta-blockers are contraindicated, not tolerated or fail to suppress symptoms, the guideline states that amiodarone, sotalol or a class 1c drug should be used (that is, as a second-line treatment). The choice of amiodarone, sotalol or a class 1c drug depends on the type of atrial fibrillation (persistent or paroxysmal) and the presence or absence of structural heart disease, left ventricular dysfunction or coronary heart disease. The manufacturer's submission considered the use of dronedarone as an alternative to amiodarone, sotalol and class 1c drugs for people in whom one of these antiarrhythmic drugs is indicated. The submission also considered the use of dronedarone as part of first-line treatment in addition to standard baseline therapy (usually including beta-blockers and anticoagulation), but only for people with a CHADS₂ score of 4 or more. The CHADS₂ score is used to estimate the risk of stroke in people with atrial fibrillation to determine whether they need treatment with anticoagulation therapy. The score is calculated by giving one point each for the presence of congestive heart failure, hypertension or diabetes mellitus, and being aged 75 years or older. Two points are given if people have already had an ischaemic stroke or transient ischaemic attack.

3.2 The main clinical evidence on dronedarone in the manufacturer's submission was based on four randomised controlled trials comparing dronedarone with placebo and one comparing it with amiodarone:

- EURIDIS and ADONIS (n = 1237, 12-month follow-up), phase III multicentre, parallel, randomised, double-blind, placebo-controlled trials. EURIDIS and ADONIS were European and non-European trials of the same design and the results were combined and reported together. Both dronedarone and placebo were given in addition to standard first-line therapy, which included beta-blockers (in about 60% of participants) and anticoagulation (in about 70% of participants).
- ATHENA (n = 4628, mean follow-up: 21 months), a phase III multicentre, parallel, randomised, double-blind, placebo-controlled trial. Both dronedarone and placebo were given in addition to standard first-line therapy, which included beta-blockers (in 71% of participants) and anticoagulation (in 60% of participants).
- DIONYSOS (n = 504, 6-month follow-up), a phase III multicentre, parallel, randomised, double-blind trial comparing dronedarone with amiodarone.

3.3 The EURIDIS and ADONIS trials included people with paroxysmal or persistent atrial fibrillation or atrial flutter, who had an episode of atrial fibrillation in the 3 months before study entry but were in sinus rhythm on entry into the study. Both trials excluded people with NYHA class III and IV heart failure. The trial population across the two trials had a mean age of 63 years, and 69% were male. Eleven per cent of people had atrial flutter, 41% had structural heart disease and 17% of people had congestive heart failure. The results showed that fewer people in the dronedarone arm had atrial fibrillation recurrence at 12 months than in the placebo group (64% and 75% respectively, hazard ratio 0.75, 95% confidence interval [CI] 0.65 to 0.87, $p < 0.001$). The median time to atrial fibrillation recurrence was 116 days in the dronedarone group and 53 days in the placebo group. In the dronedarone group, the mean ventricular rate during the first adjudicated atrial fibrillation recurrence was 103 beats per minute compared with 117 beats per minute in the

placebo group ($p < 0.001$). Most adverse events were similar between the study groups (numbers not reported), although there was a lower incidence of hyperthyroidism in the dronedarone group (8.4% and 14.1% respectively, $p = 0.002$) and a higher incidence of serum creatinine elevation (2.4% and 0.2% respectively, $p = 0.004$). A post-hoc analysis showed that 23% of people in the dronedarone groups had been admitted to hospital or had died at 12 months versus 31% in the placebo groups (hazard ratio 0.73, 95% CI 0.57 to 0.93, $p = 0.01$).

- 3.4 The ATHENA trial included people with paroxysmal or persistent atrial fibrillation or atrial flutter with at least one of the following additional risk factors for a major cardiovascular event: aged 70 years or older; hypertension needing treatment with at least two antihypertensive drugs of different classes; diabetes; previous stroke, transient ischaemic attack or systemic embolism; left atrial diameter of greater than or equal to 50 mm; left ventricular ejection fraction of less than 40%. During the course of the trial, overall mortality figures were lower than expected. As a consequence the inclusion criteria were changed so that people were required to be aged 75 years or older to be eligible, or aged 70–75 years with at least one of the previously specified risk factors, and people younger than 70 years of age were no longer eligible. People were excluded from the ATHENA trial if they had permanent atrial fibrillation, an unstable haemodynamic condition, NYHA class IV congestive heart failure or an acute myocardial infarction.
- 3.5 The ATHENA trial population had a mean age of 72 years, and 53% were male. The primary outcome was a composite of first unplanned hospitalisation because of a cardiovascular event and death before hospitalisation. This outcome occurred in 31.9% of the dronedarone group, of whom 29.3% had a first unplanned hospitalisation because of a cardiovascular event and 2.6% died before hospitalisation. The primary outcome occurred in 39.4% of

the placebo group, of whom 36.9% had a first unplanned hospitalisation because of a cardiovascular event and 2.5% died before hospitalisation. The hazard ratio for the primary composite outcome in the dronedarone group was 0.76 (95% CI 0.69 to 0.84, $p < 0.001$). There was no statistically significant difference in all-cause mortality between the dronedarone and placebo groups (5% and 6% respectively, hazard ratio 0.84, 95% CI 0.66 to 1.08, $p = 0.18$); however there were significantly fewer deaths from cardiovascular causes in the dronedarone group than the placebo group (2.7% and 3.9% respectively, hazard ratio 0.71, 95% CI 0.51 to 0.98, $p = 0.03$). A post-hoc analysis of the ATHENA trial found that dronedarone was associated with a statistically significant reduction in the risk of stroke compared with placebo (hazard ratio 0.66, 95% CI 0.46 to 0.96, $p = 0.027$). Another post-hoc analysis reported that dronedarone was associated with a statistically significant reduction in all-cause mortality compared with placebo in people with a CHADS₂ score of 4 or more (hazard ratio 0.53, 95% CI 0.31 to 0.91, $p = 0.022$).

- 3.6 In the ATHENA trial, treatment was stopped early in 30.2% of the dronedarone group compared with 30.8% of the placebo group (statistical significance not reported). The main reasons for discontinuation were: adverse events (12.7% in the dronedarone group and 8.1% in the placebo group, $p < 0.001$), participant's request (7.5% in each group), and other reasons (9.4% in the dronedarone group and 14.4% in the placebo group). Gastrointestinal events (including diarrhoea and nausea) were the most common adverse events in both groups, but were more frequent in the dronedarone than the placebo group (26.2% and 22.0% respectively, $p < 0.001$). The dronedarone group also had higher incidences of bradycardia ($p < 0.001$), QT-interval prolongation ($p < 0.001$), rash ($p = 0.006$) and serum creatinine elevation ($p < 0.001$) than the placebo group. There was no statistically significant difference between the dronedarone and

placebo groups in the number of serious treatment-emergent adverse events (456 and 489 in each group respectively).

- 3.7 The DIONYSOS trial included people with paroxysmal or persistent atrial fibrillation or atrial flutter in whom cardioversion and antiarrhythmic treatment were indicated and who were also receiving anticoagulation. The trial population had a mean age of 64 years, and two-thirds were male. The primary composite outcome of first incidence of either recurrence of atrial fibrillation or premature study discontinuation because of intolerance or lack of efficacy occurred in 75.5% of the dronedarone group and 58.8% of the amiodarone group (hazard ratio 1.59, $p < 0.0001$). This difference was mainly because of the higher incidence of recurrence of atrial fibrillation in the dronedarone group than in the amiodarone group (63.5% and 42.0% respectively). The main safety endpoint was defined as the incidence of thyroid-, hepatic-, pulmonary-, neurological-, skin-, eye- or gastrointestinal-specific events, or early study drug discontinuation after any adverse event. This endpoint occurred in 39.3% of the dronedarone group after 12 months of treatment compared with 44.5% in the amiodarone group (hazard ratio 0.80, 95% CI 0.60 to 1.07, $p = 0.13$). Dronedarone was associated with lower incidences of adverse drug reactions including thyroid dysfunction, significant bradycardia and effects on the central nervous system. There were two (0.8%) deaths in the on-treatment period in the dronedarone group compared with five (2.0%) in the amiodarone group (the causes of the deaths were provided but marked academic in confidence).
- 3.8 The manufacturer carried out direct and indirect analyses and a mixed treatment comparison of dronedarone compared with amiodarone, sotalol and class 1c drugs (flecainide and propafenone combined) and of each antiarrhythmic drug compared with placebo. The analyses were conducted for five outcomes: atrial fibrillation recurrence, all-cause mortality, treatment

discontinuation, treatment discontinuation because of adverse events and stroke. The meta-analysis demonstrated that atrial fibrillation recurrence was significantly lower with all antiarrhythmic drugs compared with placebo and that dronedarone was the least effective of all antiarrhythmic drugs (odds ratios were marked academic in confidence). The mixed treatment comparison indicated that dronedarone was associated with a lower risk of all-cause mortality than amiodarone (odds ratio 3.19, 95% CI 1.16 to 8.76, $p = 0.032$) and sotalol (odds ratio 5.05, 95% CI 1.84 to 13.87, $p = 0.009$). There was no statistically significant difference in all-cause mortality between dronedarone and placebo and not enough evidence to compare dronedarone with class 1c drugs. The mixed treatment comparison showed that dronedarone was associated with a lower risk of stroke than placebo (odds ratio 1.44, 95% CI 1.19 to 1.76, $p = 0.015$), but there was no difference between dronedarone and sotalol or amiodarone. However, this analysis was based on limited data.

- 3.9 The manufacturer provided information on two trials of dronedarone that were outside its licensed indication and that therefore did not form the main evidence base for the submission. These were the ERATO trial, in people with permanent atrial fibrillation, and the ANDROMEDA trial, in people with severe heart failure. In addition, the manufacturer submitted results of an analysis of safety using pooled data from five placebo-controlled dronedarone trials (ATHENA, EURIDIS and ADONIS plus two additional trials that did not meet inclusion criteria for the main clinical-effectiveness review: ERATO and DAFNE). The analysis included a total of 6285 people and the average duration of dronedarone exposure was 12 months. The main adverse events associated with dronedarone were diarrhoea, nausea or vomiting, serum creatinine elevation, rash, and cardiac events (bradycardia and QT prolongation). The incidence of serious adverse events was similar in the dronedarone and placebo groups (18.0% and 19.7% respectively) and these

were mainly related to infections and infestations, gastrointestinal disorders, and cardiac disorders. There were more early discontinuations in the dronedarone group than the placebo group (11.8% and 7.7% respectively) and the most common reason for stopping dronedarone was diarrhoea (statistical significance not reported).

- 3.10 The model used in the manufacturer's cost-effectiveness analysis was a discrete event simulation that predicts a person's course if they are treated with dronedarone compared with the predicted course with alternative treatment pathways. The manufacturer stratified people depending on their type of atrial fibrillation and baseline risk factors into five groups in accordance with the NICE guidance on atrial fibrillation (NICE clinical guideline 36): paroxysmal atrial fibrillation without structural heart disease, paroxysmal atrial fibrillation with coronary heart disease, paroxysmal atrial fibrillation with left ventricular dysfunction, persistent atrial fibrillation without structural heart disease, and persistent atrial fibrillation with structural heart disease. For each of these subgroups, the manufacturer evaluated the cost effectiveness of dronedarone at two positions in the care pathway for atrial fibrillation (see section 3.1). When dronedarone was evaluated as part of a first-line treatment for people with a CHADS₂ score of 4 or more (in addition to standard baseline therapy), the comparator was standard baseline therapy alone (including beta-blockers [excluding sotalol] and anticoagulation). When dronedarone was evaluated as a second-line treatment option, the comparators were the antiarrhythmic drugs amiodarone, sotalol and class 1c drugs, depending on the type of atrial fibrillation and baseline risk factors described above.
- 3.11 The manufacturer's model used a lifetime time horizon and included four health states: normal sinus rhythm, permanent atrial fibrillation with uncontrolled symptoms, permanent atrial fibrillation

with controlled symptoms and death. From the normal sinus rhythm state, people could move to any of the other states. From the two permanent atrial fibrillation health states, people could move between these states or to death. Transition between health states was determined by the following events: atrial fibrillation recurrence, acute coronary syndrome, stroke, congestive heart failure, treatment discontinuation, change in symptoms (for the permanent atrial fibrillation states) or death. The baseline risk of these events was taken from the ATHENA trial, extrapolated to a lifetime time horizon and adjusted for each treatment arm using odds ratios from the mixed treatment comparison. All-cause mortality was estimated using age-specific UK life tables (from the Government Actuary's Department) and adjusted for CHADS₂ score. The risk of death after stroke and congestive heart failure events was estimated using published sources.

- 3.12 The model included adverse events associated with each treatment. Adverse event rates for dronedarone were taken from a pooled analysis of the six dronedarone trials (DAFNE, ADONIS, ERATO, EURIDIS, ATHENA and DIONYSOS), for amiodarone they were taken from the DIONYSOS trial, and for sotalol and class 1c drugs they came from the SPCs. Utilities for the health states were taken from the AFTER cohort of the European Heart Survey on atrial fibrillation. The disutilities associated with adverse events were taken from a study undertaken by the manufacturer (n = 127) using a time trade-off approach.
- 3.13 In the model, drug costs for comparators were taken from the 'British national formulary' (edition 57). Doses were based on the recommended dosage stated in the SPCs. Drug administration costs were sourced from NHS Reference Costs 2007–08. For dronedarone these consisted of a specialist outpatient visit for treatment initiation and a GP visit for a day-7 creatinine test (£213). For comparators, it was assumed that hospitalisation was required

for treatment initiation (£249) and 6-monthly GP visits and tests were required for monitoring (£58–76 depending on the treatment). Costs for the majority of health events occurring in the model were taken from published literature. Most events were assumed to incur a one-off cost; but for stroke and congestive heart failure, ongoing daily costs were assumed. Costs for adverse events came from NHS Reference Costs 2007–08. A proportion of adverse events were assumed to require hospitalisation (based on expert clinical opinion) and the rest were assumed to require an outpatient consultant visit. For short-term adverse events, a one-off cost at treatment initiation was incurred and for adverse events with lifetime effects, a 6-monthly GP visit was assumed to be required. Data on resource use were sourced from clinical opinion and published literature.

- 3.14 In the manufacturer's base-case analysis, the incremental cost-effectiveness ratios (ICERs) for the analysis of dronedarone if given in addition to standard baseline therapy (for people with a CHADS₂ score of 4 or more) compared with standard baseline therapy alone ranged from £6757 to £7890 per quality-adjusted life year (QALY) gained (incremental costs £3053 and £3307 and incremental benefits 0.45 and 0.42 QALYs for these two ICERs respectively). The ICERs varied depending on the type of atrial fibrillation and the presence of structural heart disease, coronary heart disease or left ventricular dysfunction. For the analysis of dronedarone as an alternative antiarrhythmic drug to amiodarone, the ICERs were £2645 per QALY gained (incremental cost £3528 and incremental benefit 1.33 QALYs) for paroxysmal atrial fibrillation with left ventricular dysfunction and £3113 per QALY gained (incremental cost £3986 and incremental benefit 1.28 QALYs) for persistent atrial fibrillation with structural heart disease. For the comparison of dronedarone with class 1c drugs, the ICERs were £20,003 per QALY gained (incremental cost £1980 and incremental benefit 0.10 QALYs) for paroxysmal atrial fibrillation with no structural heart

disease and £20,761 per QALY gained (incremental cost £2069 and incremental benefit 0.10 QALYs) for persistent atrial fibrillation with no structural heart disease. For the comparison of dronedarone with sotalol, the ICERs ranged from £1929 to £2197 per QALY gained (incremental costs £3986 and £4384 and incremental benefits 2.07 and 2.00 QALYs for these two ICERs respectively) (depending on the type of atrial fibrillation and the presence or absence of underlying heart disease).

3.15 The manufacturer conducted a number of sensitivity analyses including:

- subgroup analyses based on CHADS₂ scores and gender
- using alternative sources for the baseline distribution of CHADS₂ score
- varying the model time horizon
- assuming a minimum mortality benefit from dronedarone relative to its comparators by using the lower end of the 95% CI of the mortality estimate for comparators and the upper end of the 95% CI for dronedarone (rather than the point estimates), and vice versa (that is, assuming a maximum relative mortality benefit from dronedarone)
- using different curve fits for the modelled clinical events such as stroke and treatment discontinuations
- using different estimates for various parameters including mortality treatment effect, stroke treatment effect, treatment discontinuation, adverse event rate, costs of dronedarone and utilities.

The analyses that had the greatest effect on the ICERs were using a 1-year time horizon (rather than a lifetime time horizon) and assuming a minimum mortality benefit from dronedarone relative to its comparators.

3.16 The ERG considered that all relevant trials of dronedarone had been included in the manufacturer's submission. It noted that the ATHENA trial included people who were older and had a higher risk of a major cardiovascular event than people in the other trials and that the application of this evidence to a lower-risk and younger population was uncertain. The ERG commented that the DIONYSOS trial was the only head-to-head trial of dronedarone versus an antiarrhythmic drug and therefore the relative efficacy of dronedarone compared with antiarrhythmic drugs other than amiodarone was unknown. It also noted that the DIONYSOS trial was short-term (minimum follow-up: 6 months). The ERG commented on a number of limitations of the meta-analyses and mixed treatment comparison in the manufacturer's submission. These included:

- a lack of consideration of clinical and statistical heterogeneity of the studies included in the analyses
- uncertainty about the validity of pooling the individual studies in the different analyses
- few events in the studies
- the use of outcomes that were neither pre-specified endpoints nor centrally adjudicated
- inconsistencies in the selection of studies across the different analyses
- the restriction of randomised controlled trials in the mixed treatment comparison.

The ERG considered that the assumption that class 1c drugs have a similar effect on all-cause mortality to dronedarone and no effect on the risk of stroke (made because of a lack of evidence) might not be valid. It noted an inconsistency in the direction of effect between results of the direct and indirect analyses and the mixed treatment comparison for the outcome of treatment discontinuations because of any cause. The ERG considered that

the existing clinical evidence across the antiarrhythmic drugs appeared most robust for the outcome of atrial fibrillation recurrence, but considerably more uncertain for the other major clinical endpoints such as stroke and all-cause mortality. The ERG also noted that although the marketing authorisation for dronedarone states that it should be used to lower ventricular rate, there was little evidence presented on this outcome.

3.17 The ERG considered that in general, the manufacturer's approach to the economic evaluation met the requirements of the NICE reference case, had an appropriate structure for the decision problem, and was of high quality, overall. However, the ERG noted a number of issues with the cost-effectiveness analysis, including concern over the pivotal assumption of mortality benefit:

- The treatment pathways evaluated by the manufacturer might not represent the full range of treatment strategies or sequences for dronedarone.
- The baseline data from the ATHENA trial, used in the model, might not be generalisable to people with atrial fibrillation in the NHS because they came from an older and higher-risk population.
- The results of the meta-analyses and mixed treatment comparisons, used in the model, might not be appropriate because of concerns about the methodology of these analyses.
- The lack of health-related quality-of-life data from any of the dronedarone studies.
- The assumption of lower initiation and monitoring costs for dronedarone compared with other antiarrhythmic drugs might not be appropriate.
- The uncertainty associated with modelling the benefits of dronedarone over the longer term because of the short duration of the trials.

- 3.18 The ERG made revisions to the manufacturer's model to correct coding errors (relating to adverse events costs and the length of time that mortality treatment benefits were applied). The revisions resulted in considerably lower ICERs than those reported in the manufacturer's base case for the comparisons of dronedarone with sotalol and amiodarone (ICERs ranged from £1895 to £4014 per QALY gained in the ERG's analysis applying a lifetime mortality benefit compared with £1980 to £8142 per QALY gained in the base case). The results for dronedarone compared with class 1c drugs were unaffected because both drugs were assumed to have the same mortality benefit.
- 3.19 The ERG stated that the manufacturer's base-case ICERs were based on the estimates of relative effectiveness of dronedarone compared with other antiarrhythmic drugs derived from the manufacturer's mixed treatment comparison. It had previously noted concerns about this mixed treatment comparison (section 3.16). The ERG therefore performed a number of analyses exploring the impact of assumptions about treatment effects on the ICERs. These included:
- assuming that dronedarone has the same effect on mortality across all CHADS₂ subgroups (for the comparison of dronedarone with standard baseline therapy)
 - assuming that sotalol and amiodarone have no effect on mortality, but keeping the assumed mortality benefit of dronedarone
 - assuming that class 1c drugs, sotalol and amiodarone have the same effect on mortality as dronedarone
 - assuming that class 1c drugs have a more beneficial effect on mortality than dronedarone
 - assuming that class 1c drugs have the same effect on stroke as dronedarone

- using effect estimates from a reanalysis of the mixed treatment comparison of all-cause mortality using a wider range of studies than that used in the manufacturer's analysis.

3.20 For most analyses, the ICERs increased but remained below £20,000 per QALY gained. However, when sotalol and amiodarone were assumed to have the same effect on mortality as dronedarone, the ICERs increased to between £55,063 and £119,704 per QALY gained. When class 1c drugs were assumed to have the same effect on the risk of stroke as dronedarone, the ICERs approximately doubled (to about £38,000 per QALY gained) and when class 1c drugs were assumed to have greater mortality benefits than dronedarone, class 1c drugs had both higher effectiveness and lower costs than dronedarone. The ERG also explored the uncertainty around treatment initiation, monitoring costs and utility weights used in the model. The impact on the ICERs for all analyses and comparisons was marginal.

3.21 The ERG conducted exploratory analyses to identify the main drivers of the cost-effectiveness results. The first was to explore the effect on the ICERs when all treatment effects are excluded from the economic analysis except atrial fibrillation recurrence. The ICERs either increased to between £1,355,984 and £70,323,846 per QALY gained or dronedarone was shown to have both higher costs and lower effectiveness than the comparators. The ERG then explored the effect on the ICERs when the treatment effects on all-cause mortality were included in the analysis in addition to atrial fibrillation recurrence. The ICERs decreased to between £1815 and £4566 per QALY gained for the comparisons of dronedarone with standard baseline therapy, sotalol and amiodarone. For the comparison of dronedarone with class 1c drugs, the ICERs were either £370,690 or dronedarone was shown to have both higher costs and lower effectiveness than the comparators (because both drugs were assumed to have the same effect on mortality). Based

on these analyses, the ERG concluded that the main driver of the cost effectiveness of dronedarone compared with standard baseline therapy, sotalol or amiodarone is the reduction in all-cause mortality associated with dronedarone. To explore the main driver of the cost effectiveness of dronedarone compared with class 1c drugs, the ERG conducted a further analysis including the treatment effects on stroke in addition to atrial fibrillation recurrence and mortality. This resulted in ICERs of £43,543 and £46,500 per QALY gained. The ERG noted that when treatment effects on adverse events were included in the analysis (as in the manufacturer's base-case analysis), the ICERs were around £18,000 per QALY gained. It therefore advised that the combined effect of reduced risk of stroke and fewer adverse events was the main driver of cost effectiveness for dronedarone compared with class 1c drugs.

- 3.22 After consultation on the first appraisal consultation document (ACD), the ERG conducted two further scenario analyses in which the treatment effects on all-cause mortality were varied. In the first analysis, dronedarone was assumed to have no effect on all-cause mortality compared with placebo, whereas amiodarone, sotalol and class 1c drugs were assumed to increase the risk of all-cause mortality (using effect estimates from the ERG's mixed treatment comparison). For the comparison of dronedarone with standard baseline therapy (in people with a CHADS₂ score of 4 or more), the ICERs increased from the ERG's revised base case (between £3358 and £4014 per QALY gained) to between £56,798 and £69,575 per QALY gained. For the comparisons with amiodarone and sotalol, the ICERs increased from between £1692 and £2349 to between £2588 and £5853 per QALY gained and for the comparison with class 1c drugs, the ICERs were lower (£11,648 and £12,760 per QALY gained) than in the ERG's revised base case (£18,206 and £18,955 per QALY gained). In the second analysis, amiodarone, sotalol and class 1c drugs were assumed to

have no effect on all-cause mortality compared with placebo, and the effect of dronedarone compared with placebo was varied from an odds ratio of 0.84 (that is, a beneficial effect as in the manufacturer's model) to 1.0 (that is, no effect on all-cause mortality). This threshold analysis showed that when the odds ratio was 0.95 or lower (that is, when dronedarone was assumed to reduce all-cause mortality by at least 5%), the ICERs for all comparisons were between £9323 and £20,689 per QALY gained.

- 3.23 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA197

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dronedarone, having considered evidence on the nature of atrial fibrillation and the value placed on the benefits of dronedarone by people with the condition, those who represent them, and clinical specialists. It considered comments received at consultation on the ACDs. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the positions for dronedarone in the treatment pathway for atrial fibrillation proposed by the manufacturer. It noted that the NICE guidance on atrial fibrillation (NICE clinical guideline 36) states that a standard beta-blocker should be the initial treatment for people with symptomatic atrial fibrillation (in addition to anticoagulation) and that an antiarrhythmic drug should be used when beta-blockers fail to control symptoms or are contraindicated (that is, as a second-line treatment). The Committee initially discussed using dronedarone in addition to standard baseline therapy of beta-blockers and anticoagulation (that is, as a first-line treatment). It noted that the manufacturer had only presented cost-effectiveness evidence at this position in the

care pathway for the subgroup of people with a CHADS₂ score of 4 or more (that is, people with a high risk of stroke). The Committee also noted that the licensed indication for dronedarone was to prevent recurrence of atrial fibrillation or to lower ventricular rate, but that the only outcome that was presented in this subgroup was all-cause mortality. The Committee then discussed the use of dronedarone as an alternative antiarrhythmic drug for second-line treatment of atrial fibrillation and considered that the comparators assessed in the manufacturer's submission (sotalol, class 1c drugs and amiodarone) were appropriate.

4.3 The Committee considered that not all possible uses of dronedarone had been evaluated in the manufacturer's submission. It heard from clinical specialists and patient experts that a potential use of dronedarone would be in people who are unable to tolerate other antiarrhythmic drugs, in particular amiodarone. However, no evidence was provided relating to the clinical effectiveness and adverse effects of dronedarone in this group of people.

4.4 The Committee understood from clinical specialists and patient experts that they considered amiodarone to be an effective antiarrhythmic drug for controlling atrial fibrillation symptoms, but that it had a high level of toxicity and many people were not able to tolerate it. The clinical specialists and patient experts commented that antiarrhythmic treatment options for people with atrial fibrillation are limited and they would welcome an antiarrhythmic drug that was effective at controlling atrial fibrillation symptoms and that was more tolerable than amiodarone. The Committee also heard from patient experts that younger people, who cannot take class 1c drugs or sotalol, might benefit from an antiarrhythmic drug that is more tolerable than amiodarone because of the longer length of time that they are likely to need treatment. It discussed comments received at consultation stating that younger people with atrial fibrillation who also had congenital heart problems would

value dronedarone as a treatment option. However, the Committee concluded that because no evidence was presented for people with congenital heart disease, it could not make any recommendations specifically in this group.

- 4.5 The Committee considered it appropriate that dronedarone is initiated by a specialist in a secondary care setting, which clinical specialists commented is usual practice for second-line treatment with antiarrhythmic drugs. The Committee noted that the cost-effectiveness model submitted by the manufacturer assumed that treatment with dronedarone was initiated by a specialist during an outpatient visit.

Clinical effectiveness

- 4.6 The Committee discussed the evidence on the effect of dronedarone on atrial fibrillation recurrence. It considered that the randomised controlled trials (ATHENA, EURIDIS, ADONIS and DIONYSOS) demonstrated that dronedarone was more effective than placebo at reducing atrial fibrillation recurrence, but less effective than amiodarone. It discussed the results of the meta-analyses and mixed treatment comparison conducted by the manufacturer that indicated that all antiarrhythmic drugs, including dronedarone, were effective at reducing atrial fibrillation recurrence, but that dronedarone was the least effective. The Committee concluded that dronedarone reduced atrial fibrillation recurrence compared with placebo, but that it appeared to be less effective for atrial fibrillation recurrence than other antiarrhythmic drugs.
- 4.7 The Committee discussed the evidence on the effect of dronedarone on ventricular rate. It noted that the licensed indication for dronedarone was to prevent recurrence of atrial fibrillation or to lower ventricular rate, but that the only studies that assessed ventricular rate in people with non-permanent atrial fibrillation were the EURIDIS and ADONIS trials. It noted that these trials reported a lower ventricular rate in the dronedarone group than the placebo

group. The Committee was also aware that ventricular rate was not included in the manufacturer's economic model. It heard from clinical specialists that the ERATO trial had shown that dronedarone reduces ventricular rate compared with placebo. However, the Committee noted that this study was in people with permanent atrial fibrillation, which is not a licensed indication for dronedarone. The Committee considered that there was insufficient evidence to reach a definitive conclusion about the benefits of dronedarone for reducing ventricular rate in people with non-permanent atrial fibrillation.

- 4.8 The Committee discussed the trial evidence on the effect of dronedarone on mortality. It considered the results of the ATHENA trial, which reported lower cardiovascular mortality in the dronedarone group compared with the placebo group but no statistically significant difference in all-cause mortality (for the whole trial population). The Committee concluded that a reduction in all-cause mortality with dronedarone compared with placebo had not been demonstrated by the ATHENA trial for the whole trial population. The Committee discussed the post-hoc subgroup analysis of the ATHENA trial that reported a lower risk of all-cause mortality in the dronedarone group compared with the placebo group for people with a CHADS₂ score of 4 or more. It discussed the use of the CHADS₂ score to predict mortality. It heard from clinical specialists that the CHADS₂ score was a useful method of assessing stroke risk in people with atrial fibrillation to determine the need for anticoagulation treatment, but that it was not used to predict mortality. It noted published evidence that reported an association between CHADS₂ score and risk of all-cause mortality for people who have had a stroke. However, the Committee considered that no evidence had been presented to validate the use of CHADS₂ score for more generally predicting all-cause mortality in people with atrial fibrillation.

- 4.9 The Committee discussed the issue of all-cause mortality in relation to the DIONYSOS trial, which provided the only direct head-to-head comparison of dronedarone with another antiarrhythmic drug, and reported fewer deaths in the dronedarone group than in the amiodarone group. However, the Committee noted the short follow-up of the trial and the small number of deaths in the study, and it considered whether all the deaths in the amiodarone group were because of cardiovascular causes (noting that the causes of death were marked commercial in confidence). Therefore the Committee considered that no conclusion about the relative effect of dronedarone and amiodarone on mortality could be made on the basis of this trial.
- 4.10 The Committee discussed the results of the manufacturer's mixed treatment comparison, which reported a lower risk of all-cause mortality for dronedarone compared with placebo. It noted the ERG's criticism about the methodology used for the mixed treatment comparison. It also noted that the CIs for this analysis crossed the null effect value, indicating that the difference was not statistically significant. The Committee considered that the mixed treatment comparison was largely based on the difference in all-cause mortality between the treatment arms in the ATHENA trial, which itself was not statistically significant. The Committee concluded that there was considerable uncertainty about the effect of dronedarone on all-cause mortality. It was not persuaded that a reduction in the risk of all-cause mortality for dronedarone compared with placebo had been demonstrated by the mixed treatment comparison.
- 4.11 The Committee then discussed the evidence on the risk of all-cause mortality for the other antiarrhythmic drugs. It noted results from the mixed treatment comparison showing that sotalol and amiodarone were associated with a higher risk of mortality than placebo. It discussed the results of the ERG's reanalysis of the

mixed treatment comparison and also considered evidence from two published meta-analyses of antiarrhythmic drugs. The Committee noted that all of these analyses reported a trend towards increased all-cause mortality with sotalol and amiodarone compared with placebo, albeit less than that reported in the manufacturer's mixed treatment comparison. It also noted that only the hazard ratio for the comparison of sotalol with placebo for all-cause mortality had a CI that did not cross 1.0, indicating a statistically significant difference between these drugs. The Committee was aware that there were limited data on class 1c drugs. It considered comments received at consultation and from the clinical specialists that amiodarone, sotalol and class 1c drugs were associated with an increased risk of mortality. Overall, the Committee accepted that the risk of mortality with the other antiarrhythmic drugs was likely to be higher than with dronedarone.

- 4.12 The Committee considered the evidence on the effect of dronedarone on the risk of stroke. It heard from clinical specialists that stroke was a known complication of arrhythmias such as atrial fibrillation. Therefore, drugs that are more effective in reducing atrial fibrillation might be expected to have a greater long-term benefit in relation to stroke prevention. The Committee discussed the post-hoc analysis of the ATHENA trial and noted that the ATHENA investigators concluded that 'the observation of a reduced rate of stroke in patients receiving dronedarone cannot be considered a definitive conclusion'. It discussed the mixed treatment comparison that resulted in reduced risk of stroke with dronedarone compared with placebo. It noted that this analysis was based on a small number of studies with very few events and no studies had any prospective collection of data on stroke incidence. The Committee concluded there was considerable uncertainty about the effect of dronedarone on the risk of stroke. It was not persuaded that a reduction in the risk of stroke with dronedarone compared with other antiarrhythmic drugs had been demonstrated.

4.13 The Committee discussed the adverse events associated with dronedarone. It was aware of the ANDROMEDA trial in which dronedarone was associated with an increased risk of mortality in people with severe congestive heart failure and noted that having atrial fibrillation was not an inclusion criterion for this trial. It was also aware that the SPC states that dronedarone is contraindicated in people with unstable NYHA class III and IV heart failure, and that it is not recommended in people with stable, recent NYHA class III heart failure and people with left ventricular ejection fraction less than 35%. The Committee noted that the most common adverse events reported across the trials of dronedarone were gastrointestinal. It discussed the possibility of serious adverse events such as pulmonary fibrosis, thyroid disease and torsades de pointes (an arrhythmia). It noted that there were very few cases reported in the randomised controlled trials, but that these trials were all relatively short term. The Committee considered evidence from the DIONYSOS trial that showed that people in the dronedarone group had fewer adverse events than those in the amiodarone group. However, it noted that these results were also based on short-term data. It noted there was no direct evidence comparing the adverse effects of dronedarone with sotalol or class 1c drugs. The Committee heard from patient experts that they did not consider that the adverse events associated with dronedarone would impact significantly on quality of life for people with atrial fibrillation. It noted comments from patients and clinical specialists received during consultation on the first ACD that all current antiarrhythmic drugs had side effects that had a significant impact on quality of life, but particularly amiodarone, with long-term use. Overall, the Committee concluded that the adverse effect profile of dronedarone was likely to be more favourable than amiodarone.

4.14 The Committee specifically considered the balance between the better short-term side-effect profile and the lower effectiveness of

dronedarone compared with amiodarone. It heard from patient experts that some people with atrial fibrillation might prefer to take an antiarrhythmic drug that has better tolerability, despite it having less effect on atrial fibrillation recurrence. It also heard that effectiveness of an antiarrhythmic drug for reducing atrial fibrillation recurrence and its tolerability could be more important to some people with atrial fibrillation than longer-term benefits such as a reduction in the risk of stroke or death. The Committee was aware of the potential value placed on dronedarone by patients when it examined the cost-effectiveness analyses.

Cost effectiveness

4.15 The Committee discussed the economic analysis provided by the manufacturer. It noted the ERG's conclusion that the approach used was, in general, appropriate and in accordance with the NICE reference case. However, the Committee was concerned about some of the key assumptions in the model, in particular that there was a beneficial effect of dronedarone on mortality and that the ATHENA trial was an appropriate source of data for the baseline risk of events. It also had concerns about the modelled costs of dronedarone and other antiarrhythmic drugs and the utilities used in the model. In addition, the Committee noted that the economic analysis was based on pair-wise comparisons of two treatments and did not use incremental analyses to compare all treatments simultaneously. It also noted that the economic analysis did not evaluate all possible uses of dronedarone.

4.16 The Committee discussed the use of the placebo arm of the ATHENA trial to inform the baseline event rates in the model. It considered that this was based on an assumption that the ATHENA population was representative of people with atrial fibrillation in the UK. The Committee noted that the ATHENA trial included people who were older and had higher cardiovascular risk than people in the other dronedarone trials. It considered that the ATHENA

population represented a higher-risk group than the more general population of people with atrial fibrillation in the UK in whom dronedarone would be used. Therefore, the Committee concluded that the cost-effectiveness estimates it had been presented with were only relevant to the population represented by the ATHENA trial (that is, people with additional cardiovascular risk).

- 4.17 The Committee noted that in the manufacturer's base-case analysis, the ICERs ranged from £1900 to £20,800 per QALY gained depending on the type of atrial fibrillation, the presence of structural heart disease, left ventricular dysfunction and coronary heart disease, and the comparator. It considered the ERG's revisions to the model to be appropriate, involving correction of coding errors and use of a lifetime time horizon for mortality benefits, which resulted in decreased ICERs ranging from £1700 to £19,000 per QALY gained. However, it noted that these figures did not incorporate changes in other key assumptions such as the mortality benefit associated with dronedarone.
- 4.18 The Committee discussed the ERG's analyses exploring the main factors that influenced the cost effectiveness of dronedarone. It considered that the relative effect of dronedarone and antiarrhythmic drugs on mortality was a key factor in the economic analysis. It again considered comments received during consultation on the first ACD and from the clinical specialists about the likely excess mortality associated with other antiarrhythmic drugs. In light of the uncertainty about the effect of dronedarone on mortality, the Committee discussed several exploratory scenario analyses conducted by the ERG in which the relative all-cause mortality effects of each antiarrhythmic drug were varied. It considered the scenario in which dronedarone had no effect on mortality compared with placebo, and other antiarrhythmic drugs were associated with some increase in mortality (as calculated in the ERG's meta-analysis), to be the most appropriate, given the

uncertainty about the mortality effect of dronedarone. It noted the ICERs from this analysis were below £15,000 per QALY gained for the use of dronedarone as a second-line treatment alternative to sotalol, class 1c drugs and amiodarone. It also noted the ICERs from this analysis were above £50,000 per QALY gained for the use of dronedarone as part of first-line treatment in addition to standard baseline therapy (in people with a CHADS₂ score of 4 or more). The Committee concluded that these cost-effectiveness estimates were the most plausible of all those presented.

- 4.19 The Committee discussed the costs and utilities included in the economic analysis. It noted that lower initiation and monitoring costs were attributed to dronedarone than other antiarrhythmic drugs. The Committee also noted the ERG's criticism that the utilities used in the model appeared to exceed general population values for healthy states. It considered the ERG's analyses that used revised drug administration costs and utilities, and concluded that these changes had a marginal impact on the cost-effectiveness estimates of dronedarone.
- 4.20 The Committee noted comments received at consultation on the first ACD that the economic analysis had not taken into account the potential cost savings of the reduced cardiovascular hospitalisations associated with dronedarone (shown in the ATHENA trial). It considered that the costs and effects of hospitalisation were included in the analysis through the modelling of events such as atrial fibrillation recurrence and stroke for which hospitalisation costs may be incurred. The Committee also considered comments received at consultation on the first ACD that treatment with dronedarone would be stopped if it was not effective and this was not considered in the economic evaluation. It noted that the submission provided by the manufacturer did not specifically evaluate treatment stopping rules and also did not consider the full range of potential treatment sequences for

dronedarone. However, the Committee considered that some element of treatment discontinuation had been accounted for in the modelling of withdrawal because of adverse events or lack of efficacy.

4.21 In light of the above considerations, the Committee discussed the cost effectiveness of dronedarone as a first-line treatment for atrial fibrillation (in addition to standard baseline therapy usually including beta-blockers). It noted that cost-effectiveness evidence for dronedarone as a first-line therapy had only been provided for the subgroup of people with a CHADS₂ score of 4 or more. In addition to concerns about the validity of the CHADS₂ score in this context, the Committee considered that the beneficial effect of dronedarone on all-cause mortality assumed in the manufacturer's submission was not proven. It noted that when this effect was removed from the economic analysis the cost per QALY gained was above £50,000. The Committee concluded that the use of dronedarone in people with a CHADS₂ score of 4 or more (in addition to standard baseline therapy) for the first-line treatment of atrial fibrillation could not be considered a cost-effective use of NHS resources. The Committee also noted that no evidence had been provided for first-line treatment with dronedarone other than in people with a CHADS₂ score of 4 or more. Therefore it could not make any conclusions about the first-line use of dronedarone in other people with non-permanent atrial fibrillation. The Committee concluded that dronedarone could not be recommended as a first-line treatment for atrial fibrillation (in addition to standard baseline therapy usually including beta-blockers).

4.22 The Committee discussed the cost effectiveness of dronedarone as a second-line treatment for people whose atrial fibrillation is not controlled by standard baseline therapy (that is, as an alternative to the antiarrhythmic drugs: amiodarone, sotalol and class 1c agents). It considered that a beneficial effect of dronedarone on all-cause

mortality was not proven; however, it accepted that the risk of mortality with the other antiarrhythmic drugs was likely to be higher than with dronedarone. It considered that when this scenario was modelled, the costs per QALY gained were within an acceptable range. The Committee noted that these cost-effectiveness estimates were largely based on data from the ATHENA trial, which included people who had a higher risk of a major cardiovascular event, and it was uncertain whether these data were applicable to people in England and Wales who would receive second-line treatment for atrial fibrillation. Therefore the Committee concluded that using dronedarone as a second-line alternative to amiodarone, class 1c drugs, or sotalol for the treatment of non-permanent atrial fibrillation could be considered a cost-effective use of NHS resources in people who have the same characteristics as the population in the ATHENA trial, that is, they have at least one of the following additional cardiovascular risk factors: hypertension requiring drugs of at least two different classes, diabetes, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter at least 50 mm, left ventricular ejection fraction less than 40% or age 70 years or older. The Committee was mindful that there might be some overlap between people with cardiovascular risk factors and those in whom dronedarone is contraindicated (with unstable NYHA class III or IV heart failure) or not recommended (with left ventricular ejection fraction less than 35%). Therefore the Committee considered it important to emphasise in its recommendations that dronedarone should not be used in people with unstable NYHA class III or IV heart failure and to refer to the recommendation in the SPC about the use of dronedarone in people with left ventricular ejection fraction less than 35%.

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA197).
- Costing report and costing template to estimate the savings and costs associated with implementation.
 - Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 The Committee considered that research directly comparing antiarrhythmic drugs would be valuable, in particular assessing the relative effect of the different antiarrhythmic drugs on clinical outcomes and mortality.

7 Related NICE guidance

- Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36
- Percutaneous radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 168 (2006). Available from www.nice.org.uk/guidance/IPG168

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in March 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
August 2010

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Brian Buckley

Lay member

Mark Campbell

Director of Standards, Bury Primary Care Trust

Professor Usha Chakravarthy

Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Professor Peter Clark (Chair)

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor in Health Economics, University of Sheffield

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology

Dr Jon Fear

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh

Senior Lecturer and Honorary Consultant, University of Liverpool

Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carole Haigh

Professor in Nursing, Manchester Metropolitan University

Dr Kevin Hardy

Consultant Physician, St Helens and Knowsley Teaching Hospitals NHS Trust

Alison Hawdale

Lay member

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Pro Vice Chancellor for Research and Enterprise, Keele University
Professor of Statistics, Keele University

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis

Practice Development Manager, Manchester Primary Care Trust

Professor Jonathan Michaels (Vice Chair)

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

GP, Tramways Medical Centre

Professor Oluwafemi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Mike Pinkerton

Chief of Business Development – The Rotherham NHS Foundation Trust

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Philip Rutledge

Consultant Public Health and Health Policy, NHS Lothian

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Mr Paddy Storrie

Lay member

Dr Cathryn Patricia Thomas

GP and Associate Professor, The University of Birmingham

Mr Mike Wallace

Health Economics and Reimbursement Director, Johnson & Johnson Medical

Dr Lok Yap

Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

B ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sally Gallagher

Technical Lead

Bhash Naidoo

Technical Adviser

Kate Moore

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), University of York:

- Claire McKenna, et al. Dronedarone for atrial fibrillation and atrial flutter, October 2009.

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation documents (ACDs). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I and II also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Sanofi-Aventis

II Professional/specialist and patient/carer groups:

- British Association of Stroke Physicians
- British Cardiovascular Society
- British Heart Foundation
- Coronary Prevention Group
- Heart Rhythm UK
- Primary Care Cardiovascular Society
- Royal College of Nursing
- Royal College of Physicians
- Society of Cardiothoracic Surgery of Great Britain and Ireland
- Arrhythmia Alliance
- Atrial Fibrillation Association
- SADS UK – The Ashley Jolly SAD Trust

III Other consultees:

- Department of Health
- Hounslow Primary Care Trust

- Welsh Assembly Government
- IV Commentator organisations (did not provide written evidence and without the right of appeal):
- CRD, CHE, University of York
 - Commissioning Support Appraisals Service
 - Department of Health, Social Services and Public Safety – Northern Ireland
 - Heart Failure Research Group, University of Glasgow
 - Medicines and Healthcare Products Regulatory Agency
 - NHS Quality Improvement Scotland
 - National Clinical Guideline Centre for Acute and Chronic Conditions
 - NIHR Coordinating Centre for Health Technology Assessment
- C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on dronedarone by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.
- Dr Andreas Wolff, nominated by the Primary Care Cardiovascular Society – clinical specialist
 - Dr Uday Trivedi, nominated by the Society for Cardiothoracic Surgery – clinical specialist
 - Dr Neil Sulke, nominated by Heart Rhythm UK – clinical specialist (provided written statement only)
 - Mrs Jo Jerrome, nominated by Arrhythmia Alliance – patient expert
 - Mrs Eileen Porter, nominated by Atrial Fibrillation Association – patient expert
- D Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.
- Sanofi-Aventis