CEDAC FINAL RECOMMENDATION

DRONEDARONE HYDROCHLORIDE
(Multaq – sanofi-aventis Canada Inc.)
Indication: Reduction in Cardiovascular Hospitalizations due to Atrial Fibrillation

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that dronedarone not be listed.

Reasons for the Recommendation:
1. At the confidential price submitted, the cost of dronedarone is up to [redacted] times greater than amiodarone and it is uncertain if dronedarone has a therapeutic advantage compared with amiodarone since in one double blind randomized controlled trial, serious adverse events and withdrawals due to adverse events were similar between dronedarone and amiodarone. The confidential price was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

2. While in one double-blind randomized controlled trial dronedarone reduced hospitalizations due to atrial fibrillation compared with placebo, rhythm outcomes were not reported and in another double-blind randomized controlled trial comparing dronedarone with amiodarone, statistically significant improvements in rhythm outcomes favoured amiodarone. In addition, quality of life was not reported in the dronedarone trials.

Background:
Dronedarone has a Health Canada indication for the treatment of patients with a history of, or current, atrial fibrillation, to reduce the risk of cardiovascular hospitalization due to atrial fibrillation. Dronedarone is an antiarrhythmic agent. The recommended daily dose in adults is 400 mg orally twice daily, and it is available in 400 mg tablets.

Summary of CEDAC Considerations
The Committee considered the following information prepared by the CDR: a systematic review of double-blind randomized controlled trials (RCTs) of dronedarone and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials

The CDR systematic review included six manufacturer-sponsored, double-blind, multicentre, superiority RCTs; five of which were placebo-controlled and one that compared dronedarone with amiodarone.

- DIONYSOS (N = 504) is an unpublished double-blind RCT comparing dronedarone 400 mg twice daily for six months with amiodarone 600 mg daily for 28 days followed by 200 mg daily for six months in patients with persistent atrial fibrillation (i.e., documented for more than 72 hours). Patients with chronic atrial fibrillation (i.e., more than 12 months) were excluded. Patients who remained in atrial fibrillation between day 10 and day 28, post-treatment, underwent cardioversion.
- ATHENA (N = 4,628) is a double-blind RCT comparing dronedarone 400 mg twice daily with placebo for 12 months. Patients enrolled in ATHENA had either atrial fibrillation or atrial flutter, and were required to be in sinus rhythm or undergo cardioversion. These patients were also relatively older and more sick compared with those in other dronedarone trials, and many had a history of New York Heart Association (NYHA) class II or III congestive heart failure or stroke. ATHENA was the only included study designed to measure cardiovascular-related hospitalizations or death.
- ERATO (N = 185) is a double-blind RCT comparing dronedarone 400 mg twice daily with placebo for six months. This was the only study that enrolled patients with permanent symptomatic atrial fibrillation (i.e., greater than six months), for whom cardioversion was not considered an option.
- DAFNE (N = 270) is a double-blind, randomized, placebo-controlled, dose-ranging study that evaluated dronedarone 400 mg, 600 mg, or 800 mg given twice daily for six months in patients with persistent atrial fibrillation. On day five to day eight, post-treatment patients still in atrial fibrillation underwent cardioversion.
- ADONIS (N = 629) and EURIDIS (N = 615) had the same study design. Both were double-blind RCTs that enrolled patients with atrial fibrillation or atrial flutter. Patients were randomized to either dronedarone 400 mg twice daily or placebo for 12 months.

Of these six trials, the Committee discussions focused on DIONYSOS, the active-controlled trial, and ATHENA, the large placebo-controlled trial reporting on cardiovascular hospitalizations.

Concomitant medications that were allowed included oral anticoagulants, beta blockers (excluding sotalol), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, digitalis, calcium channel blockers, statins, and antiplatelet agents.

Withdrawals in patients receiving dronedarone were significantly higher compared with amiodarone in the DIONYSOS study (39% versus 27% respectively). Withdrawals ranged from 11% to 31% across treatment groups in the placebo-controlled trials, and were similar between dronedarone and placebo groups.

Outcomes

The primary outcome in the DIONYSOS study was a composite outcome defined as the time to recurrence of atrial fibrillation, or premature discontinuation of treatment due to intolerance or lack of efficacy. The primary outcome in the ATHENA study was also a composite outcome,

defined as the time to first hospitalization due to cardiovascular events or time to death. Rhythm outcomes were not reported for ATHENA. In the remaining studies, the primary outcome was either recurrence of atrial fibrillation (DAFNE, ADONIS, and EURIDIS) or change in heart rate (ERATO).

Other outcomes were defined a priori in the CDR systematic review protocol. Of these outcomes, the Committee discussed the following: mortality, morbidity, and overall hospitalizations. None of the trials measured quality of life.

Results

Efficacy or Effectiveness

Dronedarone versus Amiodarone:

- In the DIONYSOS study, mortality was similar between the dronedarone and amiodarone groups (0.8% versus 2% respectively).
- Hospitalizations were not a pre-specified outcome in DIONYSOS and no hospitalization data were reported.
- The primary outcome of the DIONYSOS study favoured amiodarone over dronedarone [hazards ratio (HR) = 1.59, 95% confidence interval (CI): 1.27 to 1.98]. Atrial fibrillation recurrence was statistically significantly higher in the dronedarone group compared with the amiodarone group [64% versus 42%, relative risk (RR): 1.51, 95% CI: 1.27 to 1.80]. More patients discontinued dronedarone than amiodarone because of lack of efficacy (21.3% versus 5.5% respectively, RR = 3.9, 95% CI: 2.2 to 6.8).

Dronedarone versus Placebo:

- The primary outcome was achieved in the ATHENA study; the time to first hospitalization due to cardiovascular events or time to death from any cause was statistically significantly longer in the dronedarone group compared with placebo [HR = 0.76, 95% CI: 0.68 to 0.84, P < 0.001)]. The reduction in cardiovascular hospitalizations was primarily driven by a reduction in atrial fibrillation-related hospitalizations.
- In the ATHENA study, death from any cause was similar between the dronedarone and the placebo groups (6.0% versus 5.0%). This was consistent with a CDR pooled analysis of mortality from the five placebo-controlled trials [odds ratio (OR) = 0.84, 95% CI: 0.65 to 1.08].
- In addition to the ATHENA study, the only other hospitalization data available comes from the ADONIS and EURIDIS studies. The rate of hospitalization was not a pre-specified outcome in these studies. Statistically significant reductions in time to all-cause hospitalizations or death favouring dronedarone over placebo were observed in the EURIDIS study (HR = 0.66, 95% CI: 0.47 to 0.93, P = 0.02, 32.0% versus 21.2% respectively), but not in the ADONIS study (HR = 0.80, 95% CI: 0.56 to 1.14, P = 0.22, 29.8% versus 24.5%).
- All included placebo-controlled trials found that dronedarone was statistically significantly better than placebo with respect to time to first recurrence of an episode of atrial fibrillation.

Harms (Safety and Tolerability)

Dronedarone versus Amiodarone:

- In the DIONYSOS study, there were similar proportions of patients in the dronedarone and amiodarone groups reporting total adverse events (61% versus 68% respectively) and withdrawals due to adverse events (12.9% versus 17.8% respectively).
- The proportion of patients with serious adverse events was similar between dronedarone and amiodarone groups (13.7% versus 14.5% respectively).
- The proportion of patients with thyroid events (1.2% versus 8%) and neurological events (1.2% versus 9.4%) was statistically significantly lower in the dronedarone group compared with the amiodarone group respectively, but the proportion of patients with gastrointestinal events was statistically significantly higher for dronedarone versus amiodarone (13.7% versus 7% respectively). Skin and eye adverse events were similar between the two groups. No pulmonary events were observed in either the dronedarone or amiodarone groups.

Dronedarone versus Placebo:

- In a CDR pooled analysis of the five placebo-controlled trials, serious adverse events and adverse events were similar between the dronedarone and placebo groups.
- In a CDR pooled analysis of the five placebo-controlled trials, withdrawals due to adverse events were statistically significantly higher in the dronedarone group compared with the placebo group (RR = 1.51, 95% CI: 1.30 to 1.76)

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis based on the ATHENA study, comparing dronedarone with placebo in patients ≥ 75 years of age or ≥ 70 years of age with one or more risk factors for cardiovascular morbidity. In addition, the manufacturer also provided a cost-utility analysis based on an indirect (mixed treatment) comparison, comparing dronedarone with amiodarone, sotalol, and flecainide.

Given there is a head-to-head RCT comparing dronedarone with amiodarone (DIONYSOS), which suggests similar or improved outcomes with amiodarone, and because harms were not considered in the economic model, the Committee gave more consideration to the costs of dronedarone and comparators. At the confidential price submitted, the daily cost of dronedarone ($[redacted]; 800 mg) is [redacted] to [redacted] times greater than amiodarone ($1.03 to $2.06; 200 mg to 400 mg). Dronedarone also costs more than sotalol ($1.30 to $1.96; 120 mg to 160 mg twice daily) or flecainide ($0.79 to $2.37; 50 mg to 150 mg twice daily). The confidential price of dronedarone was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Other Discussion Points:

- The Committee discussed that current management of patients with atrial fibrillation is aimed at improving quality of life, controlling heart rate, and, in a symptomatic subgroup of patients, restoring sinus rhythm, which were outcomes that were not measured in the ATHENA trial.

- The Committee considered that amiodarone is the most appropriate comparator when pharmacological cardioversion is thought to be appropriate; however, ATHENA is a placebo-controlled trial.
- It was noted that although thyroid events and neurological events were lower for dronedarone compared with amiodarone, there are no clinical trials allowing for a comparison of the long-term benefits or harms of dronedarone versus amiodarone, including stroke, pulmonary edema, and proarrhythmic effects.
- The Committee discussed that dronedarone is most likely to be used in patients with permanent atrial fibrillation, however, with the exception of the ERATO study, these patients were excluded from dronaderone trials.
- The Committee discussed a restricted listing of dronedarone consistent with the ATHENA patient population.

CEDAC Members Participating:
February 17: Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Kelly Zarnke.

May 19: Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
February 17: Dr. Anne Holbrook (Vice-Chair) and Dr. Yvonne Shevchuk.

May 19: Dr. Anne Holbrook (Vice-Chair) and Dr. Ken Bassett.

Conflicts of Interest:
CEDAC members reported no conflicts of interest related to this submission.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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