Pharmacy and Wellness Review

Volume 3 | Issue 2 Article 4

July 2012

Dronedarone: An Update to a Controversial Therapy for Atrial Fibrillation

Zachary Crawford
Ohio Northern University

Sara McAllister
Ohio Northern University

Amanda Hoersten
Ohio Northern University

Jennifer Bauer
Ohio Northern University

Megan Keller
Ohio Northern University

See next page for additional authors

Dronedarone: An Update to a Controversial Therapy for Atrial Fibrillation

Authors

Zachary Crawford, Sara McAllister, Amanda Hoersten, Jennifer Bauer, Megan Keller, and David Bright

Dronedarone: An Update to a Controversial Therapy for Atrial Fibrillation

Zachary Crawford, fourth-year pharmacy student from Centerville, Ohio; Sara McAllister, fourth-year pharmacy student from Youngstown, Ohio; Amanda Hoersten, fifth-year pharmacy student from Delphos, Ohio; Jennifer Bauer, fifth-year pharmacy student from St. Marys, Pa; **Megan Keller**, PharmD '11, community pharmacy resident; David Bright, PharmD, BCACP, assistant professor of pharmacy practice

Abstract

As of 2004, it was estimated that 2.2 million Americans were diagnosed with paroxysmal or persistent atrial fibrillation (AF) resulting in one out of every six strokes in the United States. AF leads to a reduction in pumping efficiency of the heart increasing the risk of several serious sequelae such as thromboembolic stroke and congestive heart failure (CHF). It also results in a reduced quality of life for the patients suffering from the disease. Patients with AF require appropriate antiarrhythmic therapy to control symptoms and prevent adverse effects of the condition. Multaq® (dronedarone), an antiarrhythmic drug approved for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF, showed promise as an alternative to amiodarone therapy after its approval in July 2009. However, recent reports have shown that dronedarone use doubles mortality risk and serious adverse events in certain patient populations specifically those with heart failure or permanent AF. This review evaluates the research that brought dronedarone to the market and reassesses the appropriateness of its use based upon recent findings.

Introduction

Atrial fibrillation (AF), a supraventricular tachyarrhythmia, and associated atrial flutter are two of the most common clinically significant cardiac arrhythmias.[1-4] In 2004, an estimated 2.2 million Americans had paroxysmal or persistent AF, affecting roughly 0.4 percent of the general population, with an increased prevalence of greater than 6 percent in those over 80 years of age. Patients with non-rheumatic AF are two to seven times more likely to suffer an ischemic stroke than those without AF. Additionally, one in every six strokes occurs in a patient with AF. According to the Framingham study, overall stroke risk in patients aged 80 to 89 drastically increases to 23.5 percent from 1.5 percent in patients aged 50 to 59. While AF itself is not directly life threatening, it results in reduced pumping efficiency of the heart, which increases the risk of several serious sequelae including thromboembolic stroke and CHF. Quality of life measures in AF patients are drastically reduced due to multiple symptoms associated with the condition including palpitations, dyspnea, chest pain, fatigue and dizziness. However, these symptoms vary between patients.

To manage patients with AF, it is paramount to address the issues related to the arrhythmia itself and to strive for the prevention of a thromboembolism.[1,2,4] Management of dysrhythmias in patients with persistent AF can be done in two ways: restoration and maintenance of sinus rhythm or permitting AF to continue and ensuring the ventricular rate is controlled. Relief of symptoms, prevention of embolism and avoidance of cardiomyopathy are the main reasons for restoration and maintenance of sinus rhythm in patients with AF. Dysrhythmias can be managed pharmacologically or non-pharmacologically via electrical cardioversion, surgical or catheter ablation, pacing or with an internal atrial cardioverter/defibrillator.

Pharmacologically, the antiarrhythmic drug class is broken down into subcategories.[5] These include type I sodium channel blockers, which can be further divided into Ia, Ib, Ic according to dissociation rates from the sodium channels; type II beta adrenergic receptor antagonists; type III drugs that prolong the refractory period by prolonging the action potential; and type IV non-dihydropyridine calcium channel blockers. A specific drug or class should be chosen based on the cause of the arrhythmia, pharmacokinetics and patient-specific conditions. For more information on antiarrhythmic drug classes refer to Chapter 29: Anti-arrhythmic drugs in the twelfth edition of "Goodman and Gilman's the Pharmacological Basis of Therapeutics."[2]

One of the newer antiarrhythmics to come onto the market, dronedarone (Multaq® Sanofi U.S., Bridgewater, N.J.), was approved by the Food and Drug Administration (FDA) in July 2009 to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF.[6-9] This drug was formulated to mimic the effects of amiodarone, a class III antiarrhythmic agent approved for the treatment of refractory life-threatening ventricular arrhythmias; however, dronedarone was intended to have an improved safety and tolerability profile compared to amiodarone. The typical adult dosage of dronedarone is 400 mg by mouth twice daily, administered as one tablet with the morning meal and one tablet with the evening meal. It should not be used in patients with permanent AF, as this use is associated with an increased risk of death, stroke and heart failure. Additionally, dronedarone carries a boxed warning contraindicating its use in patients with New York Heart Association (NYHA) class IV heart failure, patients with symptomatic heart failure with recent decompensation and in patients in AF who cannot be cardioverted into normal sinus rhythm. Recent reports have shown that dronedarone use doubles mortality risk and serious adverse events in these patient populations. The purpose of this review is to evaluate the research that brought this drug to the market and to reassess recent findings questioning the appropriateness of its use.

Clinical Trial Evaluations

The European Trial in Atrial Fibrillation or Flutter Patients

Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and The American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) trials were evaluated by the FDA for the approval of dronedarone in the United States. Additional information gathered from the ATHENA trial also supports the use of dronedarone in AF.

EURIDIS/ADONIS (2003) The results of two identical, placebo-controlled, multicenter, double-blind, parallel group trials were published in *The New England Journal of Medicine* in late 2007.[10] The objective of these trials was to assess if dronedarone was superior to placebo for maintaining sinus rhythm after electrical, pharmacologic or spontaneous conversion from AF or atrial flutter. The two trials involved in this study were EURIDIS and ADONIS. Inclusion and exclusion criteria were deemed appropriate for each study's purpose.

The participants were randomized into either the placebo group or the dronedarone group. In order to meet 90 percent power, for both EURIDIS and ADONIS, 368 patients in the dronedarone group and 184 patients in the placebo group had to complete the trial.[10] Neither trial met power due to patients discontinuing treatment prior to completion of the study. At one year, the rates of recurrence of AF were 64.1 percent in the dronedarone group and 75.2 percent in the placebo group. The researchers concluded that dronedarone reduced the incidence of a first recurrence and the incidence of a symptomatic first recurrence within 12 months of the trial start date. Some limitations of the trials include: the lack of comparison between dronedarone and other medications, resulting in the inability to compare adverse events and efficacy; the inability to detect every episode of recurrent arrhythmia; the exclusion criteria was extensive and may not be realistic in a normal practice setting; and patients who received amiodarone previously could be enrolled in the trial immediately after discontinuing the drug.

ATHENA (2008) The results of the ATHENA study were published in *The New England Journal of Medicine* in early 2009.[11] ATHENA assessed the effects of dronedarone on cardiovascular events in patients with AF or atrial flutter. The trial was a randomized, double-blind, placebo-controlled study conducted in 37 countries. Inclusion and exclusion criteria were deemed appropriate for the study's purpose.

The trial enrolled a total of 4,628 patients who were randomized to either the dronedarone group or the placebo group.[11] Out of the 2,301 patients receiving dronedarone, 734 (31.9 percent) experienced a primary outcome event (i.e., hospitalization due to cardiovascular events or death). Of the 2,327 receiving placebo, 917 (39.4 percent) had a primary outcome event. In order to meet a statistical power of 80 percent, the researchers estimated that 2,150 patients per group were necessary. This trial did not meet power due to over 30 percent of the patients in the dronedarone group and the placebo group discontinuing the trial prior to the conclusion of the study. The results of ATHENA found the use of dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death in these patients. Dronedarone was found to increase the time to first recurrence of AF from 53 days with placebo to 116 days with the active drug. Some limitations of the study including lack of comparison of dronedarone to other medications, the inability to detect every episode of recurrent arrhythmia and the large discontinuation rate of the dronedarone group (30.2 percent) may have limited the data regarding rates of adverse events (Table 1).

While studies have shown support for dronedarone in AF patients, several studies have brought its use into question, specifically in patients with heart failure and permanent AF.

Table 1. Important data from the trials supporting dronedarone[10,11]

	EURIDIS/ADONIS[10]	ATHENA[11]
Dronedarone dose	400 mg BID	400 mg BID
Primary endpoint(s)	Time from randomization to first documented recurrence of atrial fibrillation for at least 10 minutes	First hospitalization due to cardiovascular events or death
Secondary endpoints	Symptoms of atrial fibrillation, the mean ventricular rate during the first recurrence	Death from any cause, death from cardiovascular causes, hospitalization due to cardiovascular events
Number of patients randomized to dronedarone group	828	2301
Dronedarone patients who completed the trial	680	1605
Dronedarone hazard ratio	0.75	0.76
Significant inclusion criteria	≥ 21 years old, in sinus rhythm for at least 1 hour before randomization	≥ 70 years old, previous stroke, left ventricular ejection fraction ≤ 40%
Significant exclusion criteria	Permanent atrial fibrillation, NYHA class III or IV heart failure, use of other class I or III antiarrhythmics	Permanent atrial fibrillation, NYHA class IV heart failure, planned major surgery, use of other class I or II antiarrhythmics

ANDROMEDA (2003) The Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) was a multicenter, double-blind, placebo-controlled, randomized, parallel-group trial comparing dronedarone 400 mg twice daily with matching placebo.[12] This trial was conducted at 72 hospitals throughout several countries in Europe. The study aimed to enroll 1,000 patients to achieve a power of 90 percent with a two-sided type 2 error of 5 percent. The study was designed to specifically evaluate dronedarone with heart failure by enrolling patients classified as NYHA class III or IV heart failure. The trial measured adherence to the study by conducting a pill count at each study visit.

The primary endpoint was a composite of death from any cause and hospitalization for worsening heart failure while the secondary endpoints were death from all causes, hospitalization for cardiovascular causes or recurrence of AF.[12] Endpoints were considered to be cardiovascular unless an unequivocal non-cardiovascular cause was established. The study was initiated in June 2002, but terminated early by the safety committee in early 2003 due to an increase in death associated with the dronedarone group. At the time of termination, ANDROMEDA had enrolled 627 patients which was not enough to meet power. A total of 37 patients died during the study with 25 in the dronedarone group and 12 in placebo group (p=0.03). Very few patients reached 180 days of follow-up causing a small percentage of patients to be included in statistical analysis. While the number of deaths due to arrhythmia or sudden death was not different between the two groups, more participants died due to worsening heart failure with dronedarone compared to placebo (10 versus two respectively). Dronedarone also had a higher rate of hospitalization for cardiovascular related cause compared to the placebo arm (71 versus 50, p=0.02).

DIONYSOS (2008) 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 (DIONYSOS) was published in 2010 to compare the effectiveness of dronedarone to amiodarone in patients with persistent AF.[13] The study was conducted in 112 centers in 23 countries throughout the world between 2007 and 2008. The goal of this study was to compare the benefit/risk ratio of dronedarone and amiodarone. The combined primary endpoint was defined as recurrence of AF or premature study drug discontinuation for lack of efficacy and intolerance.

Participants with documented AF for >72 hours for whom cardioversion and antiarrhythmic treatment was deemed necessary by study investigators were enrolled. A total of 472 patients were necessary to show a relative reduction in primary endpoint of 30 percent in six months in dronedarone compared to amiodarone and a power of 80 percent with a type I error of 5 percent (two-sided). The study achieved power by enrolling 504 patients. Participants were randomized to dronedarone 400 mg twice daily or amiodarone 600 mg every day for 28 days, then 200 mg every day thereafter.

The results showed amiodarone may be superior to dronedarone in the conversion of persistent AF patients. AF recurrence following cardioversion was lower in the amiodarone group compared to the dronedarone group (24.3 percent vs. 36.5 percent respectively, p<0.001). While it is known amiodarone has many complications, including an interaction with warfarin and alteration of thyroid function, it may be superior for conversion in these patients. A high percentage of AF patients are taking warfarin for anticoagulation and this may pose a problem; however, warfarin dosing can be adjusted downward while taking amiodarone. It is also important to note the study used a lower dose of amiodarone (600 mg/day for 28 days, then 200 mg/day thereafter) compared to previous studies. The SAFE-T study used much higher dosing (800 mg/day PO for 14 days, then 600 mg/day for 14 days, then 300 mg/day for the first year and 200 mg/day thereafter) of amiodarone to show superiority to sotalol than the investigators of DIONYSOS used when comparing to dronedarone.[7,14] This may cause over inflation of recurrence rates of AF when using amiodarone in DIONYSOS, showing amiodarone may be even more superior to dronedarone.

PALLAS (2011) The Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) was a randomized, double-blind, placebo-controlled trial conducted in 489 centers throughout the world.[15] Patients enrolled had permanent AF documented with electrocardiography 14 days before randomization and six months earlier. The co-primary outcomes were composite of stroke, myocardial infarction, systemic embolism or death from cardiovascular cause and unplanned hospitalization for cardiovascular cause or death. For a power of 90 percent, 10,800 participants were needed for the trial. The study began in July 2010 and was terminated in July 2011 for safety reasons with a total of 3,236 patients enrolled.

At the time of study termination, the first co-primary outcome occurred in 43 participants in the dronedarone group compared to 19 in the placebo group (p=0.002). Participants in the dronedarone group also experienced more secondary outcomes, 127 versus 67 respectively (p<0.001). This significant increase in outcomes for the dronedarone arm caused the safety board to terminate the study. The dronedarone group also had a significantly higher rate of death including death from cardiovascular causes, such as arrhythmia, and higher rate of unplanned cardiovascular hospitalization compared to the placebo group.

PALLAS shows that dronedarone should not be used in patients with permanent AF due to a much higher incidence of adverse effects. It may be more important to control rate and prevent thrombosis in patients with permanent AF than to administer an antiarrhythmic. The longer a patient is in AF, the lower the chances of cardioversion with either pharmacological or non-pharmacological treatment.

Current Dronedarone Trials

The Effect of Addition of Dronedarone to Standard Rate Control Therapy on Ventricular Rate During Persistent Atrial Fibrillation (AFRODITE) is currently underway to assess

whether the addition of dronedarone to existing conventional rate control leads to a reduced ventricular rate after one week of dronedarone treatment in patients with a high heart rate at rest during AF.[16] This is a phase IV study comparing the addition of dronedarone to a beta blocker, calcium channel blocker or digoxin in an effort to reduce heart rate. The study was completed in November 2011, but data is not available at the time of this publication.

Several other studies evaluating the efficacy of dronedarone are currently underway. Dronedarone pattern of use in patients scheduled for elective cardioversion (ELECTRA) is a multi-center study in Canada evaluating patients with persistent AF who are undergoing elective cardioversion.[17] The objective of this study is to compare the rate of recurrence with dronedarone to placebo within six months. Data have not yet been released, even though the trial was expected to be completed in 2011. The effects of dronedarone on AF burden in subjects with permanent pacemakers (HESTIA) is a randomized, multicenter study to evaluate dronedarone's effects on AF burden.[18] HESTIA was terminated before study completion, but at the time of this publication data from the study have not been released.

Dronedarone and Heart Failure

Dronedarone has a black box warning for patients with NYHA class IV heart failure or recent decompensation of heart failure requiring hospitalization.[7] This contraindication was based on an increased risk of death noted in the ANDROMEDA study; however, the early termination of the study does not allow for proper evaluation of dronedarone in heart failure. It is important to note that in ANDROMEDA up to the time of termination only 19 of 627 enrolled had class IV heart failure.[12] The majority of participants had class II (252/627) and class III (356/627). Due to the early termination, it is not possible to discern which deaths from progressive heart failure were in class II, III or IV. Conversely, in the ATHENA study, 21 percent of participants had CHF with NYHA class II or III and 12 percent had LVEF <45 percent.[11] The investigators of ATHENA claim a subgroup analysis indicates patients with CHF had a similar benefit to the entire group, but due to a small population of heart failure patients, this claim lacks substantial evidence.[11] The published data of ATHENA did not provide information on outcomes specifically for participants with heart failure. Based on information from ANDROMEDA, even though dronedarone is only contraindicated for class IV heart failure, caution should be used when administering dronedarone to patients with any class of heart failure.[12]

Discussion

Dronedarone has been controversial since the ANDROMEDA study, and its safety and efficacy profile in AF therapy has not been proven. When ANDROMEDA was prematurely terminated in 2003, the sponsor and authors continued analyses on the data, searching for explanations of its findings.[12] The study was not published until 2008, after other information on dronedarone had been released and regulatory submissions were considered. Looking into the history of dronedarone, the initial new drug application (NDA) submitted in 2005 was not approved, citing poor results from ANDROMEDA as a reason.[16] Sanofi-Aventis then reapplied in 2008, using information from DIONYSOS and ATHENA in support of dronedarone.[17] While it was approved, the advisory committee recommended that patients with advanced (NYHA class III or IV) heart failure be excluded from dronedarone therapy and a black box warning be issued. However, the package insert only lists a contraindication for class IV heart failure.

This controversy places pharmacists in a pivotal role to ensure proper pharmacologic therapy for AF. Pharmacists are crucial to drug utilization reviews and ensuring patients are receiving the best pharmacological therapy. Drug utilization reviews empower and help guide pharmacists' decisions in appropriate therapy management in AF patients. Due to the increased risk of death in heart failure patients, especially those with permanent AF, pharmacists should be weary when patients with heart failure have prescriptions for dronedarone. International normalized ratio (INR) analyses from DIONYSOS showed that dronedarone did not have as significant an effect on INR levels compared to amiodarone, indicating that dronedarone should be considered for patients on warfarin with AF.[13] However, due to substantial information on adjusting warfarin dosing with amiodarone, pharmacists should not exclude using amiodarone with warfarin. Finally, it is important that pharmacists help to educate physicians and other clinicians about the possible serious consequences if dronedarone is not used properly.

AF results in an increased burden on quality of life, specifically in older patients. This population is often faced with a poor prognosis in terms of venous thromboemboli and mortality secondary to worsening comorbidities such as heart failure, coronary artery disease and hypertension. Control of AF is typically achieved through rate or rhythm control and anticoagulation. Dronedarone, a pharmacological agent used for rate control, is currently indicated to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF. However, due to findings from the trials studied, the safety and efficacy of dronedarone is in question. ANDROMEDA showed that dronedarone should not be used in patients with NYHA class IV heart failure and may not be safe in patients with NYHA class II and III heart failure.[12] PALLAS indicated dronedarone is not safe in patients with permanent AF leading to its contraindication in such patients.[15] DIONYSOS compared dronedarone to amiodarone for use in patients with persistent AF, but showed amiodarone may be superior to dronedarone in this situation.[13] It is possible dronedarone may be used for patients with lone AF with no other complicating factors.

Conclusion

Dronedarone was approved in 2009 as an alternative to amiodarone for the treatment of AF. However, the safety and efficacy of dronedarone has still not been proven following several recent studies. Additional studies in progress should help to identify the place in practice for this agent. Pharmacists should take great caution when using dronedarone in patients with NYHA class II, III and IV heart failure, as well as patients with permanent AF.

References

1. Sanoski CA, Bauman JL (2011). Chapter 25. The Arrhythmias. In J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey (Eds), *Pharmacotherapy: A Pathophysiologic Approach*, 8e. Retrieved January 16, 2012 from www.accesspharmacy.com/content.aspx?aID =7972803.
2. Brunton LL, Chabner BA, Knollmann BC (2011). Chapter 29. Antiarrhythmic drugs. Brunton LL, Blumenthal DK, Murri N, and Hilal-Dandan R, Knollmann BC (Eds), Goodman and Gilman's the Pharmacological Basis of Therapeutics, 12e. Retrieved April 1, 2012 from www.accesspharmacy.com.polar.onu.edu/content.aspx?ID=16668583.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults – national implications for rhythm management and stroke prevention: the AnTicoagulation and risk factors in atrial fibrillation (ATRIA) Study. *JAMA.* 2001;285: 2370-5.
4. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for management of patients with atrial fibrillation – executive summary. *Circulation.* 2006;114:700-52.
5. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for management of patients with atrial fibrillation: executive summary – a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines and policy conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) Developed in collaboration with the American Society of Pacing and Electrophysiology. *Circulation* 2001;104:2118-50.
6. Dronedarone [monograph on the Internet]. Tampa (FL): Gold Standard/Elsevier; 2012 [cited 2012 Feb 26]. Available from: www.clinical pharmacology-ip.com/Forms/search.aspx?s=dronedarone.
7. Amiodarone [monograph on the Internet]. Tampa (FL): Gold Standard/ Elsevier; 2012 [cited 2012 Feb 26]. Available from: www.clinical pharmacology-ip.com/Forms/drugoptions.aspx?cpnum=25&n= Amiodarone.
8. Husten L. Experts disagree on when to use dronedarone (Multaq). *Cardiobrief* [serial on the Internet] 2010. Accessed: February 26, 2012. Available from: cardiobrief.org/2010/04/06/experts-disagree-on-when-to-use-dronedarone-multaq/.
9. Carlson M. Rate vs rhythm control and suppression algorithms for the management and prevention of atrial fibrillation. Medscape cardiology [serial on the Internet] 2004;8(2). Accessed: February 26, 2012. Available from: www.medscape.org/viewarticle/487849.
10. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009;360:668-77.
11. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kower PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med.* 2007;357:987-99.
12. Kober L, Torp-Pedersen C, McMurray JJV, Gotzsche O, Levy S, Crijns H, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med.* 2008;358:2678-87.
13. Le Heuzey JV, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. 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 Electr.* 2010;21:597-605.
14. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med.* 2005 May 5;352(18):1861-72.
15. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, et al. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med.* 2011;365:2268-76.
16. Clinical Trials [database on the Internet]. Bethesda (MD): National Library of Medicine. 2012 [cited 2012 Mar 31]. Available from: clinicaltrials.gov/ct2/results?term=dronedarone.
17. Temple, Robert (Department of Health & Human Services, Food and Drug Administration, Rockville, MD). Letter to: Nancy Barone Kribbs (Drug Regulatory Affairs, Sanofi-Aventis U.S. Inc., Malvern, PA). 2006 Aug 29. 3 leaves. Located at: www.accessdata.fda.gov/drugsatfda_docs /nda/2009/022425s000TOC.cfm.
18. Stockbridge, Norman (Division of Cardio-Renal Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD). Divisional Memo to: Division of Cardio-Renal Drug Products (Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD). 2009 Mar 27. 2 leaves. Available from: www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022425s000 TOC.cfm.