

IMPLEMENTING HEALTH REFORM

Advanced Primary Care Practice Demo Project

The patient-centered medical home, which has been promoted by primary care organizations for decades, is finally getting some attention under the Affordable Care Act.

The concept, which calls for greater coordination of care and a team-based approach, is one of several care delivery improvement ideas being tested under the new health law.

This summer, government officials are accepting applications from federally qualified health centers to be part of a 3-year demonstration project. The project, which will run from September 2011 through August 2014, is designed to figure out what resources health centers need to become successful medical homes that improve care and reduce costs.

Under the Federally Qualified Health Center Advanced Primary Care Practice demonstration project, the federal government will pay health centers a monthly care management fee for each eligible Medicare beneficiary that receives primary care services, on top of their regular Medicare payments. In exchange, health centers must pursue Level 3 patient-centered medical home recogni-

tion through the National Committee for Quality Assurance. The project is being run jointly by the Centers for Medicare and Medicaid Services and the Health Resources Services Administration.

CMS and HRSA will spend \$42 million over 3 years to fund up to 500 health centers under the project.

Dr. Roland A. Goertz, the president of

MULTAQ® (dronedaron) Tablets

Rx Only

Brief Summary of Prescribing Information

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic [see Contraindications (4)].

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone [see Clinical Studies (14.3) in the full prescribing information].

1 INDICATIONS AND USAGE

MULTAQ is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted [see Clinical Studies (14) in the full prescribing information].

2 DOSAGE AND ADMINISTRATION

The only recommended dosage of MULTAQ is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal. Treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (e.g., ketoconazole) must be stopped before starting MULTAQ [see Contraindications (4)].

4 CONTRAINDICATIONS

MULTAQ is contraindicated in patients with:

- NYHA Class IV heart failure or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic [see Boxed Warning and Clinical Studies (14.3) in the full prescribing information]
- Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- Concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir [see Drug Interactions (7.2)]
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine anti-psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- QTc Bazett interval ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].
- Nursing mothers [see Use in Specific Populations (8.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Patients with New or Worsening Heart Failure during Treatment

Postmarketing cases of new onset and worsening heart failure have been reported during treatment with Multaq. Advise patients to consult a physician if they develop signs or symptoms of heart failure such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

5.2 Liver Injury

Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post-marketing setting. Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. It is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

5.3 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.4 QT Interval Prolongation

Dronedaron induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation [see Clinical Pharmacology (12.2) in the full prescribing information and Clinical Studies (14.1) in the full prescribing information]. If the QTc Bazett interval is ≥500 ms, MULTAQ should be stopped [see Contraindications (4)].

5.5 Increase in Creatinine after Treatment Initiation

Serum creatinine levels increase by about 0.1 mg/dL following dronedaron treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient's new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine's tubular secretion, with no effect upon the glomerular filtration rate.

5.6 Women of Childbearing Potential

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedaron caused fetal harm in animal studies at doses equivalent to recommended human doses. Women of childbearing potential should be counseled regarding appropriate contraceptive choices taking into consideration their underlying medical conditions and lifestyle preferences [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following safety concerns are described elsewhere in the label:

- New or worsening heart failure [see Warnings and Precautions (5.1)]
- Liver Injury [see Warnings and Precautions (5.2)]
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics [see Warnings and Precautions (5.3)]
- QT prolongation [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

The safety evaluation of dronedaron 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated, 3282 patients with MULTAQ 400 mg twice daily, and 2875 with placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

In clinical trials, premature discontinuation because of adverse reactions occurred in 11.8% of the dronedaron-treated patients and in 7.7% of the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.2% versus 1.8% in the placebo group) and QT prolongation (1.5% versus 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

Table 1 displays adverse reactions more common with dronedaron 400 mg twice daily than with placebo in AF or AFL patients, presented by system organ class and by decreasing order of frequency. Adverse laboratory and ECG effects are presented separately in Table 2.

Table 1: Adverse Drug Reactions that Occurred in at Least 1% of Patients and Were More Frequent than Placebo

	Placebo (N=2875)	Dronedaron 400 mg twice daily (N=3282)
Gastrointestinal		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
General		
Asthenic conditions	5%	7%
Cardiac		
Bradycardia	1%	3%
Skin and subcutaneous tissue		
Including rashes (generalized, macular, maculo-papular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic	3%	5%

Photosensitivity reaction and dysgeusia have also been reported at an incidence less than 1% in patients treated with MULTAQ.

The following laboratory data/ECG parameters were reported with MULTAQ 400 mg twice daily.

Table 2: Laboratory data/ECG parameters not necessarily reported as adverse events

	Placebo (N=2875)	MULTAQ 400 mg twice daily (N=3282)
Serum creatinine increased ≥10% five days after treatment initiation	21%	51%
QTc Bazett prolonged (>450 ms in males >470 ms in females)	19%	28%

Assessment of demographic factors such as gender or age on the incidence of treatment-emergent adverse events did not suggest an excess of adverse events in any particular sub-group.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MULTAQ. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: Heart failure [see Warnings and Precautions (5.1)].

Postmarketing cases of new onset and worsening heart failure have been reported during treatment with MULTAQ.

the American Academy of Family Physicians, explained how this project could shape future payment policy for primary care physicians.

CARDIOLOGY NEWS: This project sets out to test what is needed to help health centers make the transition to patient-centered medical homes. What does the existing research tell us about the necessary ingredients?

Dr. Goertz: The five most important ingredients are a true team approach to care; clinical information systems such as e-prescribing, electronic medical records,

registries for common chronic illnesses, and electronic patient access via a patient portal; training for all members of the care team in "patient self-management support" and between visit follow-up; care coordination for patients needing care outside of the medical home; and integration with community resources and the medical neighborhood.



CN: Under the project, health centers will receive a care management payment of \$6 per patient per month. Is this enough?

A successful demonstration will show improved care while maintaining or reducing costs.

DR. GOERTZ

the Medicare beneficiaries attributed to them. As grantees, the clinic sites will

also receive free technical assistance and training resources and funds to cover survey costs.

Health centers will need to make a determination if they are ready for the transformation and whether the care management fees will cover their increased costs.

The fees will not be enough to leverage change if the Federally Qualified Health Center serves only a small number of Medicare patients.

CN: How important is the adoption of electronic health records to the success of the medical home?

Dr. Goertz: The goal is to have computerized support for important clinical functions and integration so that physicians have the information they need to make the best decisions about diagnosis and management.

Electronic medical records with functions to help with prescribing, registries, e-mail, education, and home monitoring will soon be the standard of care. Whatever other changes a practice is making, they should continue the momentum needed to get to fully integrated electronic medical records at some point in the future.

Two keys to improved care will be appropriate data collection and use of that data. Electronic tools are very effective in these efforts.

CN: If this demonstration is successful, what will it mean for Medicare payments for medical home services in the future?

Dr. Goertz: This demonstration will show important additional proof of the value of the patient-centered medical home.

A successful demonstration will show improved care while maintaining or reducing costs, which should result in resources flowing to primary care practices to more appropriately pay them for providing patients the best care possible.

—Interview by Mary Ellen Schneider

DR. GOERTZ is a family physician in Waco, Tex., and the president of the AAFP.

For more information on the initiative, go to www.cms.gov/DemoProjects/EvalRpts/MD/itemdetail.asp?itemID=CMS1230016.

Hepatic: Serum hepatic enzymes and serum bilirubin increase: Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported [see *Warnings and Precautions* (5.2)].

Respiratory: Postmarketing cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported.

7 DRUG INTERACTIONS

Dronedaron is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 [see *Clinical Pharmacology* (12.3) in the full prescribing information]. Dronedaron's blood levels can therefore be affected by inhibitors and inducers of CYP 3A, and dronedaron can interact with drugs that are substrates of CYP 3A and CYP 2D6.

Dronedaron has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6. It has the potential to inhibit P-glycoprotein (P-gp) transport.

Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin [see *Drug Interactions* (7.1)].

In clinical trials, patients treated with dronedaron received concomitant medications including beta-blockers, digoxin, calcium antagonists (including those with heart rate-lowering effects), statins and oral anticoagulants.

7.1 Pharmacodynamic Interactions

Drugs prolonging the QT interval (inducing Torsade de Pointes)

Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics) is contraindicated because of the potential risk of Torsade de Pointes-type ventricular tachycardia [see *Contraindications* (4)].

Digoxin

Digoxin can potentiate the electrophysiologic effects of dronedaron (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedaron was co-administered with digoxin. Gastrointestinal disorders were also increased. Because of the pharmacokinetic interaction [see *Drug Interaction* (7.3)] and possible pharmacodynamic interaction, reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

Calcium channel blockers

Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedaron's effects on conduction.

Give low doses of calcium channel blockers initially and increase only after ECG verification of good tolerability [see *Drug Interactions* (7.3)].

Beta-blockers

In clinical trials, bradycardia was more frequently observed when dronedaron was given in combination with beta-blockers.

Give low dose of beta-blockers initially, and increase only after ECG verification of good tolerability [see *Drug Interactions* (7.3)].

7.2 Effects of Other Drugs on Dronedaron

Ketoconazole and other potent CYP 3A inhibitors

Repeated doses of ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedaron exposure and a 9-fold increase in C_{max} . Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated [see *Contraindications* (4)].

Grapefruit juice

Grapefruit juice, a moderate inhibitor of CYP 3A, resulted in a 3-fold increase in dronedaron exposure and a 2.5-fold increase in C_{max} . Therefore, patients should avoid grapefruit juice beverages while taking MULTAQ.

Rifampin and other CYP 3A inducers

Rifampin decreased dronedaron exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort with dronedaron because they decrease its exposure significantly.

Calcium channel blockers

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedaron exposure by approximately 1.4- to 1.7-fold [see *Drug Interactions* (7.1, 7.3)].

Pantoprazole

Pantoprazole, a drug that increases gastric pH, did not have a significant effect on dronedaron pharmacokinetics.

7.3 Effects of Dronedaron on Other Drugs

Statins

Dronedaron increased simvastatin/simvastatin acid exposure by 4- and 2-fold, respectively. Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gp inhibitors such as dronedaron.

Calcium channel blockers

Dronedaron increases calcium channel blocker (verapamil, diltiazem or nifedipine) exposure by 1.4- to 1.5-fold [see *Drug Interactions* (7.1)].

Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range

Dronedaron can increase plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with a narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-blockers and other CYP 2D6 substrates

Dronedaron increased propranolol exposure by approximately 1.3-fold following single dose administration. Dronedaron increased metoprolol exposure by 1.6-fold following multiple dose administration [see *Drug Interaction* (7.1)]. Other CYP 2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedaron.

P-glycoprotein substrates

Digoxin

Dronedaron increased digoxin exposure by 2.5-fold by inhibiting the P-gp transporter [see *Drug Interactions* (7.1)].

Dabigatran

Exposure to dabigatran is higher when it is administered with dronedaron than when it is administered alone (1.7- to 2-fold).

MULTAQ® (dronedaron) Tablets

Other P-gp substrates are expected to have increased exposure when co-administered with dronedaron.

Warfarin and losartan (CYP 2C9 substrates)

Losartan

No interaction was observed between dronedaron and losartan.

Warfarin

When healthy subjects were administered dronedaron 600 mg twice daily, exposure to S-warfarin was higher than when warfarin was administered alone (1.2-fold). Exposure to R-warfarin was unchanged and there were no clinically significant increases in INR.

More patients experienced clinically significant INR elevations (≥ 5) usually within 1 week after starting dronedaron vs. placebo in patients taking oral anticoagulants in ATHENA. However, no excess risk of bleeding was observed in the dronedaron group.

Postmarketing cases of increased INR with or without bleeding events have been reported in warfarin-treated patients initiated on dronedaron. Monitor INR after initiating dronedaron in patients taking warfarin.

Theophylline (CYP 1A2 substrate)

Dronedaron does not increase steady state theophylline exposure.

Oral contraceptives

No decreases in ethinylestradiol and levonorgestrel concentrations were observed in healthy subjects receiving dronedaron concomitantly with oral contraceptives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications* (4)]

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, dronedaron was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

When pregnant rats received dronedaron at oral doses greater than or equal to the MRHD (on a mg/m^2 basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club feet). When pregnant rabbits received dronedaron, at a dose approximately half the MRHD (on a mg/m^2 basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥ 20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m^2 basis).

Actual animal doses: rat (≥ 80 mg/kg/day); rabbit (≥ 20 mg/kg)

8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedaron and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedaron administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [see *Contraindications* (4)].

8.4 Pediatric Use

Safety and efficacy in children below the age of 18 years have not been established.

8.5 Geriatric Use

More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Efficacy and safety were similar in elderly and younger patients.

8.6 Renal Impairment

Patients with renal impairment were included in clinical studies. Because renal excretion of dronedaron is minimal [see *Clinical Pharmacology* (12.3) in the full prescribing information], no dosing alteration is needed.

8.7 Hepatic Impairment

Dronedaron is extensively metabolized by the liver. There is little clinical experience with moderate hepatic impairment and none with severe impairment. No dosage adjustment is recommended for moderate hepatic impairment [see *Contraindications* (4) and *Clinical Pharmacology* (12.3) in the full prescribing information].

10 OVERDOSAGE

In the event of overdosage, monitor the patient's cardiac rhythm and blood pressure. Treatment should be supportive and based on symptoms.

It is not known whether dronedaron or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

There is no specific antidote available.

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