

## ON THE BEAT

## Obituaries

**Dr. William Ganz**, coinventor of a revolutionary pulmonary artery catheter, died Nov. 10. He was 90 years old. A Nazi labor camp survivor, Dr. Ganz died of natural causes.

In the late 1960s, while a research scientist and staff physician at Cedars-Sinai Medical Center in Los Angeles, Dr. Ganz developed the catheter with his colleague, the late Dr. Jeremy Swan, who was chief of the medical center's cardiology division, to assess heart function in critically ill patients. In 1971, Dr. Ganz developed a new method for direct measurement of blood flow in humans, and this technique was incorporated into the Swan-Ganz catheter.

The measurement procedure, known as thermodilution, gauges the temperature difference of blood from one heart chamber to the next.

Used by more than 30 million patients since then, the balloon-tipped Swan-Ganz catheter is now standard treatment in cardiac medicine.

Inserted through a neck vein, shoulder, or groin, the device's balloon tip allows it to travel in the bloodstream. Once in place in the pulmonary artery, the catheter measures post MI effects and medication response. The device also measures cardiovascular performance of patients during heart surgery.

Born in 1919 in Kosice, Slovakia, Dr. Ganz started his medical training at Charles University in Prague. During the Nazi takeover of Czechoslovakia, Dr. Ganz was taken prisoner in a labor camp, but was later released and went into hiding in Budapest.

Dr. Ganz returned to Prague after World War II, completed his medical education, and specialized in cardiology. He began to develop his thermodilution method, but in 1966, he and his family emigrated to the United States to escape Communism. He was hired by Dr. Swan

at Cedars-Sinai.

In 1982, Dr. Ganz joined forces with Dr. Prediman K. Shaw, the current director of the Cedars-Sinai Heart Institute's cardiology division, to conduct studies of clot-dissolving therapy for myocardial infarction patients. Cedars-Sinai became the first medical center in the United States to test the therapy in humans.

The American College of Cardiology recognized Dr. Ganz with its distinguished scientist award in 1992.

Dr. Ganz was predeceased by his wife, Magda, in 2005. He is survived by his sons Tomas and Peter, and five grandchildren.

**Dr. Donald S. Baim**, an interventional cardiologist known for his work in the development of catheters and stents, died Nov. 6. He was 60 years old. His death was caused by complications of surgery for adrenal cancer.

Dr. Baim, a resident of Westwood, Mass., was chief medical and scientific officer for Boston Scientific in Natick, Mass. He had joined the company, which man-



DR. DONALD S. BAIM

ufactures pacemakers, defibrillators, and other implants, in the summer of 2006.

"He was a pioneer in the development of interventional cardiology, and the many contributions he made to science, medicine, and medical technology will serve as a proud and enduring legacy," Ray Elliott,



DR. WILLIAM GANZ

**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 dronedaron had a greater than two-fold increase in mortality. Such patients should not be given dronedaron [see Clinical Studies (14.3) in the full prescribing information].**

**1 INDICATIONS AND USAGE**

MULTAQ<sup>®</sup> 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 antipsychotics, 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**

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. There are limited data available for AF/AFL patients who develop worsening heart failure during treatment with MULTAQ. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

**5.2 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.

**5.3 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)].

**5.4 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.

**5.5 Women of Childbearing Potential**

Pre-menopausal 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)]
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics [see Warnings and Precautions (5.2)]
- QT prolongation [see Warnings and Precautions (5.3)]

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)
<b>Gastrointestinal</b>		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
<b>General</b>		
Asthenic conditions	5%	7%
<b>Cardiac</b>		
Bradycardia	1%	3%
<b>Skin and subcutaneous tissue</b>		
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%
	(N=2237)	(N=2701)
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.

**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.

## INDEX OF ADVERTISERS

<b>Actelion Pharmaceuticals US, Inc.</b> Tacleer	16a-16d, 17
<b>American College of Cardiology</b> ACC Meeting	23
<b>Astellas Pharma US, Inc.</b> Adenoscan	15-16
<b>AstraZeneca LP.</b> Atacand	25-27
<b>Daiichi Sankyo, Inc.</b> Corporate	28
<b>Forest Laboratories, Inc.</b> Bystolic	11-14
<b>Gilead Palo Alto, Inc.</b> Ranexa	19-22
<b>Otsuka America Pharmaceuticals, Inc.</b> Samsca	3-7
<b>sano-fi-aventis U.S. LLC</b> Multaq	30-32

Boston Scientific's president and CEO, said in a statement.

Born in New York and raised in Miami Beach, Dr. Baim received his undergraduate degree in physics in 1971 from the University of Chicago, and his medical degree in 1975 from Yale University School of Medicine, New Haven, Conn.

He pursued postgraduate training in medicine and cardiology at Stanford (Calif.) University, where he worked with Dr. John Simpson to develop moveable guidewire coronary angioplasty catheters. In 1981, he joined the

faculty at Harvard Medical School and established an interventional cardiology program at Beth Israel Hospital (now Beth Israel Deaconess Medical Center) in Boston. The program grew to national prominence in the refinement and application of devices such as stents. In 1994, Dr. Baim became a full professor of medicine at Harvard.

In 2000, Dr. Baim moved on to Brigham and Women's Hospital in Boston, where he directed the Center for Integration of Medicine and Innovative Technology, a nonprofit consortium of Boston teaching hospitals and engineering schools.

Dr. Baim specialized in the development and evaluation of new interventional cardiovascular devices. According to a statement from Boston Scientific, Dr. Baim "played a major role in developing technology strategies, including the assessment and partnership candidates, and their integration with internal technologies."

He was the editor of Grossman's Cardiac Catheterization, Angiography, and Intervention, and the author of more than 300 articles.

He was founder of or consultant for

more than 20 companies and medical device incubators in areas of embolic protection, thrombectomy, chronic total occlusions, arterial closure, novel stent and coatings, heart failure, and percutaneous heart valves.

Dr. Baim was remembered by his colleagues as a gifted mentor, a good friend, and a visionary in his field. He is survived by wife, Caryn Paris, sons Adam and Christopher, daughters Samantha Paris and Jenifer Pruskin, and a granddaughter, as well as his mother, Jocelyn Baim, and brother, Paul.

—Jane Locastro

Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin [see *Drug Interactions* (7.1)]. In clinical trials, patients treated with dronedarone 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 dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone 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 dronedarone'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 dronedarone 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 Dronedarone

Ketoconazole and other potent CYP 3A inhibitors

Repeated doses of ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedarone 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 dronedarone 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 dronedarone exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort with dronedarone because they decrease its exposure significantly.

Calcium channel blockers

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone 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 dronedarone pharmacokinetics.

#### 7.3 Effects of Dronedarone on Other Drugs

Statins

Dronedarone 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 dronedarone.

Calcium channel blockers

Dronedarone 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 Dronedarone 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

Dronedarone increased propranolol exposure by approximately 1.3-fold following single dose administration. Dronedarone 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 dronedarone.

Digoxin and P-glycoprotein substrates

Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter [see *Drug Interactions* (7.1)]. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone.

Warfarin and losartan (CYP 2C9 substrates)

In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR. In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. Monitor INR per the warfarin label.

No interaction was observed between dronedarone and losartan.

Theophylline (CYP 1A2 substrate)

Dronedarone does not increase steady state theophylline exposure.

Oral contraceptives

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

## MULTAQ (dronedarone) Tablets

### 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, dronedarone 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 dronedarone at oral doses greater than or equal to the MRHD (on a mg/m<sup>2</sup> 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 dronedarone, at a dose approximately half the MRHD (on a mg/m<sup>2</sup> basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses  $\geq 20$  mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m<sup>2</sup> basis).

Actual animal doses: rat ( $\geq 80$  mg/kg/day); rabbit ( $\geq 20$  mg/kg)

#### 8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedarone 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 dronedarone is minimal [see *Clinical Pharmacology* (12.3) in the full prescribing information], no dosing alteration is needed.

#### 8.7 Hepatic Impairment

Dronedarone 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 dronedarone or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

There is no specific antidote available.

Manufactured by Sanofi Winthrop Industrie

1, rue de la Vierge

33440 Ambares, France

©sanofi-aventis, 2009

All rights reserved.

MULTAQ is a trademark of sanofi-aventis.

The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC.

sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

DRO-BPLR-AS-JUL09

Revised: July 2009