

Wingspan Stent Effective in Intracranial Lesions

BY KERRI WACHTER

SAN ANTONIO — The Gateway balloon-Wingspan stent system was an effective and safe treatment option for patients with intracranial lesions with more than 50% stenosis, Dr. R. Charles Callison, Jr., said at the annual International Stroke Conference.

Dr. Callison, of the division of interventional neuroradiology at the University

of Iowa, Iowa City, used a comprehensive database of all patients undergoing endovascular treatment of symptomatic intracranial atheromatous disease (sICAD) with the Wingspan stent system during December 2005–July 2009. In all, 110 patients with 138 lesions were treated. Greater than 50% stenosis occurred in 50 lesions, followed by 70%–80% stenosis for 48 lesions, and 50%–69% for 37 lesions.

Technical success was achieved in 99%

of lesions. There were two failures to cross a balloon or stent. Acute in-stent thrombosis was noted periprocedurally in 11% of cases, all of which were successfully treated with intravenous tirofiban.

The combined major stroke and death rate in the first 30 days—a coprimary endpoint—was 5.5% (mortality 1.8%). The rate of ipsilateral stroke and death after 30 days—a coprimary endpoint—was 1.8% (no mortality). Eight minor is-

chemic events occurred; all were transient ischemic attacks.

On angiography, the initial mean stenosis rate was 77%. The postprocedure stenosis rate was 18% and 19% of lesions required post dilation.

Dr. Callison reported that he has no relevant financial relationships. One of his coinvestigators is a consultant for Boston Scientific, maker of the Wingspan stent. ■

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 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

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)]
- 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) |
|--------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------------|
| 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% |
| | (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.