

FDA Approves Biodegradable Sealant Patch

BY ALICIA AULT

The Food and Drug Administration has approved a biodegradable sealant patch, TachoSil, for cardiovascular surgery. The sealant, a dry collagen sponge coated with fibrinogen and thrombin, is manufactured by Nycomed Austria GmbH of Linz, Austria, and is already available in 30 countries.

When placed in a wound, the fibrinogen and thrombin become activated and convert into fibrin. That allows a clot to form, preventing bleeding and sealing the tissue. According to the FDA, the sponge breaks down within the body in 4-6 months. “This approval provides an additional tool for surgeons to help control mild and moderate bleeding from blood vessels during cardiovascular surgery when

standard surgical techniques are ineffective or impractical,” Dr. Karen Midthun, acting director of the FDA’s Center for Biologics Evaluation and Research, said in a statement. According to data submitted to the agency by Nycomed, TachoSil stopped bleeding within 3 minutes in 75% of 119 cardiovascular surgery patients given the sponge, vs. 33% in the control group. The FDA said that the sponge can

cause allergic reactions, but that such reactions were not statistically higher for TachoSil study patients. In data submitted to support European approval, the most common side effect was fever. The European Medicines Agency cautioned that thromboembolic complications were possible if TachoSil was unintentionally placed within a blood vessel. The FDA warned that TachoSil is not intended for such use. ■

MULTAQ
(dronedarone) 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
Dronedarone 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 dronedarone 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. Dronedarone 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 dronedarone 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 dronedarone-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 dronedarone 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.

	Placebo (N=2875)	Dronedarone 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.

	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.

7 DRUG INTERACTIONS
Dronedarone 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]. Dronedarone's blood levels can therefore be affected by inhibitors and inducers of CYP 3A, and dronedarone can interact with drugs that are substrates of CYP 3A and CYP 2D6. Dronedarone 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.