

## POLICY &amp; PRACTICE

## Lipitor Personal Injury Suits

The top-selling statin Lipitor (atorvastatin) is being blamed for causing a suicide, peripheral neuropathy, memory loss, and severe muscle damage in two suits filed against the drug's maker, Pfizer Inc., by a New York-based plaintiff's attorney, Mark Jay Krum. The complaint, filed in New York State Supreme Court, alleges that after using Lipitor for 17 months, 60-year-old Charles M. Wilson experienced peripheral neuropathy, inflammatory demyelinating polyneuropathy, and memory loss. Three years after ceasing the medication,

Mr. Wilson still has loss of balance, fatigue, and burning in his extremities, according to the suit. In the second case, 47-year-old Michael Mazzariello claimed that Lipitor use led to neuropathy, weakness in his extremities, and short-term memory loss. Both suits claim that Pfizer failed to adequately warn physicians and patients about the drug's risks. At a press briefing, another potential plaintiff alleged that Lipitor caused her teenage son to commit suicide. Pfizer said in a statement that it would "vigorously challenge in court all the baseless claims made in these lawsuits."

## Guidant Price Disclosure Sought

Advocacy group Public Citizen has filed a lawsuit in Pennsylvania federal court seeking to force the medical device maker Guidant Inc. to disclose its prices to ECRI, a nonprofit organization that collects cost-effectiveness and safety data on procedures and devices for hospitals, group purchasing organizations, health plans, and health agencies worldwide. ECRI has published a database of cardiac rhythm management devices since 1996. In 2001, Guidant, a division of Boston Scientific, began requiring customers to keep prices confidential. ECRI continued to publish the data because it was not aware of the contractual

agreement, according to the suit. After several years of silence, Guidant contacted ECRI in 2004 and asked it to immediately stop publishing the data and urged hospitals to stop supplying information—demands that have been made repeatedly under threat of litigation. The Public Citizen complaint was filed in response and alleges that ECRI's database is noncommercial speech that is protected by the First Amendment. Boston Scientific said confidentiality is an accepted practice in heart rhythm management and essential to its business. "We simply don't want the price negotiated privately with one hospital based on one set of circumstances used against us in negotiations with another hospital with an entirely different set of circumstances," said Paul Donovan, Boston Scientific senior vice president of corporate communications, in a statement.

## Licensure for Drug Sales Reps?

A proposal making its way through the Massachusetts legislature would require that pharmaceutical company sales representatives be licensed by the state and complete continuing education programs to renew that license. The proposal passed as an amendment to the state budget and was in a joint House-Senate conference report. State Senator Mark C. Montigny, a Democrat from New Bedford, has sought to pass such a licensure requirement several times over the past few years, without success. Under the latest proposal, pharmaceutical companies—and their representatives—would also be prohibited from giving gifts, entertainment, travel, honoraria, or anything of value to physicians or public officials. Violators would be subject to a \$5,000 fine and up to 2 years in jail. In a statement, Ken Johnson, senior vice president of the Pharmaceutical Research and Manufacturers Association, said that licensing was unnecessary because the Food and Drug Administration already regulates promotional and educational materials and that the legislation is wrongheaded because it "seeks to impose criminal penalties on what should be viewed as the important sharing of information between pharmaceutical companies and physicians regarding the risks and benefits of medicines."

## Survey: FDA Influenced by Politics

A majority of Americans—82%—believe the FDA is greatly influenced by politics when making decisions about the safety and efficacy of new prescription drugs, according to a Wall Street Journal online Harris Interactive poll. The finding was similar across parties, with 87% of Democrats, 77% of Republicans, and 88% of Independents saying they thought that politics outweighed science greatly or to some extent in decision making. The survey of more than 2,300 adults was conducted in mid-May. In addition, almost 60% said the agency is doing a fair or poor job in ensuring the safety and efficacy of new drugs. Only 36% said it was doing an excellent or good job. That is a reversal from 2 years ago, when 56% had a positive view and 37% a negative view of the FDA. Opinions have not changed much on the agency's performance in bringing innovative drugs to market quickly. In 2004, 62% said the FDA was not doing well on that front, compared with 70% in the latest poll.

—Alicia Ault

## Intravenous B-type natriuretic peptide (BNP) NATRECOR® (nesiritide)

## Brief Summary

NatreCOR® (nesiritide) for Injection

Rx Only

FOR INTRAVENOUS INFUSION ONLY

The following is a Brief Summary of the Full Prescribing Information for NatreCOR® (nesiritide) for Injection. Please review the Full Prescribing Information prior to prescribing NatreCOR.

## INDICATIONS AND USAGE

NatreCOR (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of NatreCOR reduced pulmonary capillary wedge pressure and improved dyspnea.

## CONTRAINDICATIONS

NatreCOR is contraindicated in patients who are hypersensitive to any of its components. NatreCOR should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure <90 mm Hg.

## WARNINGS

Administration of NatreCOR should be avoided in patients suspected of having, or known to have, low cardiac filling pressures.

## PRECAUTIONS

**General:** Parenteral administration of protein pharmaceuticals or *E. coli*-derived products should be attended by appropriate precautions in case of an allergic or untoward reaction. No serious allergic or anaphylactic reactions have been reported with NatreCOR.

NatreCOR is not recommended for patients for whom vasodilating agents are not appropriate, such as patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent upon venous return, or for patients suspected to have low cardiac filling pressures. (See CONTRAINDICATIONS.)

**Renal:** NatreCOR may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with NatreCOR may be associated with azotemia. When NatreCOR was initiated at doses higher than 0.01 mcg/kg/min (0.015 and 0.03 mcg/kg/min), there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased. In the 30-day follow-up period in the VMAC trial, 5 patients in the nitroglycerin group (2%) and 9 patients in the NatreCOR group (3%) required first-time dialysis.

**Cardiovascular:** NatreCOR may cause hypotension. In the VMAC trial, in patients given the recommended dose (2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion) or the adjustable dose, the incidence of symptomatic hypotension in the first 24 hours was similar for NatreCOR (4%) and IV nitroglycerin (5%). When hypotension occurred, however, the duration of symptomatic hypotension was longer with NatreCOR (mean duration was 2.2 hours) than with nitroglycerin (mean duration was 0.7 hours). In earlier trials, when NatreCOR was initiated at doses higher than the 2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion (i.e., 0.015 and 0.03 mcg/kg/min preceded by a small bolus), there were more hypotensive episodes and these episodes were of greater intensity and duration. They were also more often symptomatic and/or more likely to require medical intervention (see ADVERSE REACTIONS). NatreCOR should be administered only in settings where blood pressure can be monitored closely, and the dose of NatreCOR should be reduced or the drug discontinued in patients who develop hypotension (see Dosing Instructions). The rate of symptomatic hypotension may be increased in patients with a blood pressure <100 mm Hg at baseline, and NatreCOR should be used cautiously in these patients. The potential for hypotension may be increased by combining NatreCOR with other drugs that may cause hypotension. For example, in the VMAC trial in patients treated with either NatreCOR or nitroglycerin therapy, the frequency of symptomatic hypotension in patients who received an oral ACE inhibitor was 6%, compared to a frequency of symptomatic hypotension of 1% in patients who did not receive an oral ACE inhibitor.

**Drug Interactions:** No trials specifically examining potential drug interactions with NatreCOR were conducted, although many concomitant drugs were used in clinical trials. No drug interactions were detected except for an increase in symptomatic hypotension in patients receiving oral ACE inhibitors (see PRECAUTIONS, Cardiovascular).

The co-administration of NatreCOR with IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated (these drugs were not co-administered with NatreCOR in clinical trials).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility of nesiritide. Nesiritide did not increase the frequency of mutations when used in an *in vitro* bacterial cell assay (Ames test). No other genotoxicity studies were performed.

**Pregnancy: Category C:** Animal developmental and reproductive toxicity studies have not been conducted with nesiritide. It is also not known whether NatreCOR (nesiritide) can cause fetal harm when administered to pregnant women or can affect reproductive capacity. NatreCOR should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when NatreCOR is administered to a nursing woman.

**Pediatric Use:** The safety and effectiveness of NatreCOR in pediatric patients has not been established.

**Geriatric Use:** Of the total number of subjects in clinical trials treated with NatreCOR (n = 941), 38% were 65 years or older and 16% were 75 years or older. No overall differences in effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. Some older individuals may be more sensitive to the effect of NatreCOR than younger individuals.

## ADVERSE REACTIONS

Adverse events that occurred with at least a 3% frequency during the first 24 hours of NatreCOR infusion are shown in the following table.

Adverse Events	VMAC Trial		Other Long Infusion Trials		
	Nitroglycerin (n = 216)	NatreCOR Recommended Dose (n = 273)	Control* (n = 256)	0.015 (n = 253)	0.03 (n = 246)
<b>Cardiovascular</b>					
Hypotension	25 (12%)	31 (11%)	20 (8%)	56 (22%)	87 (35%)
Symptomatic Hypotension	10 (5%)	12 (4%)	8 (3%)	28 (11%)	42 (17%)
Asymptomatic Hypotension	17 (8%)	23 (8%)	13 (5%)	31 (12%)	49 (20%)
Ventricular Tachycardia (VT)	11 (5%)	9 (3%)	25 (10%)	25 (10%)	10 (4%)
Non-sustained VT	11 (5%)	9 (3%)	23 (9%)	24 (9%)	9 (4%)
Ventricular Extrasystoles	2 (1%)	7 (3%)	15 (6%)	10 (4%)	9 (4%)
Angina Pectoris	5 (2%)	5 (2%)	6 (2%)	14 (6%)	6 (2%)
Bradycardia	1 (<1%)	3 (1%)	1 (<1%)	8 (3%)	13 (5%)
<b>Body as a Whole</b>					
Headache	44 (20%)	21 (8%)	23 (9%)	23 (9%)	17 (7%)
Abdominal Pain	11 (%)	5 (4%)	10 (4%)	6 (2%)	8 (3%)
Back Pain	7 (3%)	10 (4%)	4 (2%)	5 (2%)	3 (1%)
<b>Nervous</b>					
Insomnia	9 (4%)	6 (2%)	7 (3%)	15 (6%)	15 (6%)
Dizziness	4 (2%)	7 (3%)	7 (3%)	16 (6%)	12 (5%)
Aridity	6 (3%)	8 (3%)	2 (1%)	8 (3%)	4 (2%)
<b>Digestive</b>					
Nausea	13 (6%)	10 (4%)	12 (5%)	24 (9%)	33 (13%)
Vomiting	4 (2%)	4 (1%)	2 (1%)	6 (2%)	10 (4%)

\* Includes dobutamine, milrinone, nitroglycerin, placebo, dopamine, nitroprusside, or amrinone.

Adverse events that are not listed in the above table that occurred in at least 1% of patients who received any of the above NatreCOR doses included: Tachycardia, atrial fibrillation, AV node conduction abnormalities, catheter pain, fever, injection site reaction, confusion, paresthesia, somnolence, tremor, increased cough, hemoptysis, apnea, increased creatinine, sweating, pruritus, rash, leg cramps, amblyopia, anemia. All reported events (at least 1%) are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

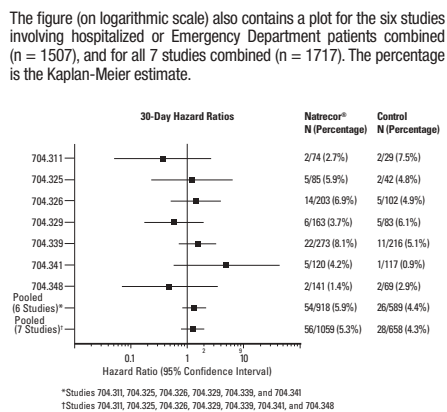
In placebo and active-controlled clinical trials, NatreCOR has not been associated with an increase in atrial or ventricular tachyarrhythmias. In placebo-controlled trials, the incidence of VT in both NatreCOR and placebo patients was 2%. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or NatreCOR Therapy) trial, the effects of NatreCOR (n = 163) and dobutamine (n = 83) on the provocation or aggravation of existing ventricular arrhythmias in patients with decompensated CHF was compared using Holter monitoring. Treatment with NatreCOR (0.015 and 0.03 mcg/kg/min without an initial bolus) for 24 hours did not aggravate pre-existing VT or the frequency of premature ventricular beats, compared to a baseline 24-hour Holter tape.

## Clinical Laboratory

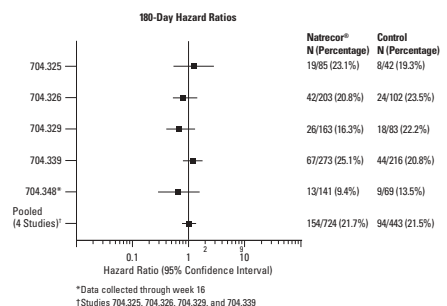
Data from all seven studies in which 30-day data were collected are presented in the chart below. The data depict hazard ratios and confidence intervals of mortality data for randomized and treated patients with NatreCOR relative to active controls through day 30 for each of the 7 individual studies (Studies 311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], and 348 [FUSION I]).

## Effect on Mortality

The figure (on logarithmic scale) also contains a plot for the six studies involving hospitalized or Emergency Department patients combined (n = 1507), and for all 7 studies combined (n = 1717). The percentage is the Kaplan-Meier estimate.



The figure below represents 180-day mortality hazard ratios for randomized and treated patients from all four individual studies where 180-day data were collected, 16 week hazard ratios for Study 348 (180-day data were not collected), and the four studies with 180-day data pooled (n = 1167).



There were few deaths in these studies, so the confidence limits around the hazard ratios for mortality are wide. The studies are also small, so some potentially important baseline imbalances exist among the treatment groups, the effects of which cannot be ascertained.

## OVERDOSAGE

No data are available with respect to overdosage in humans. The expected reaction would be excessive hypotension, which should be treated with drug discontinuation or reduction (see PRECAUTIONS) and appropriate measures.

## Distributed by:

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