

# Weight-loss wars

## A spate of deaths and a raft of lawsuits over diet drugs

BY ALICIA MUNDY

Over the 1996 Memorial Day weekend, Mary Linnen celebrated her engagement with her parents. The wedding would take place in the fall, and she had worked out all the details but one: Before she bought her wedding gown, Linnen wanted to lose 20 pounds. Her physician had prescribed a new diet-drug combination, fen-phen, and Linnen wouldn't shop for her dress until after she shed the weight.

She never bought the gown. She began suffering dizzy spells and shortness of breath and quickly stopped taking the drugs. But soon the 29-year-old tennis player and former captain of her high school swim team could hardly walk up the stairs.

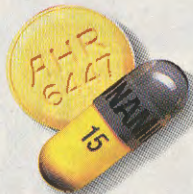
Medical tests showed Linnen had developed primary pulmonary hypertension from one of the diet drugs, her surgeon said. He inserted a tube in Linnen's chest and plugged it into a computerized box that would pump medicine to her heart. On Feb. 22, 1997, Linnen was released from a Boston hospital. Her fiancé drove her home and carried her up to her apartment. But when he put her on the bed, she cried, "Something's wrong." Linnen couldn't breathe. Her fiancé's call to 911 came too late.

"**Surprise.**" Nearly seven months after Linnen died, Pondimin, one half of the popular fen-phen combo, and Redux, a stronger version of Pondimin, were withdrawn from the market. The reason: The Food and Drug Administration had determined that the drugs could cause heart-valve problems, which medical experts say are related to pulmonary hypertension. Medical experts have since attributed more than 200 cases

of pulmonary hypertension in the United States to Pondimin and Redux. Of those, at least 40 have already resulted in death, records and interviews show.

Today, with the first of over 1,000 lawsuits involving the two drugs set for trial, questions loom. When they pulled the drugs from the market, the companies that sold them, Philadelphia-based Wyeth-Ayerst (Pondimin and Redux) and Boston-based Interneuron (Redux), issued statements indicating that the heart-valve problems had come as a "surprise."

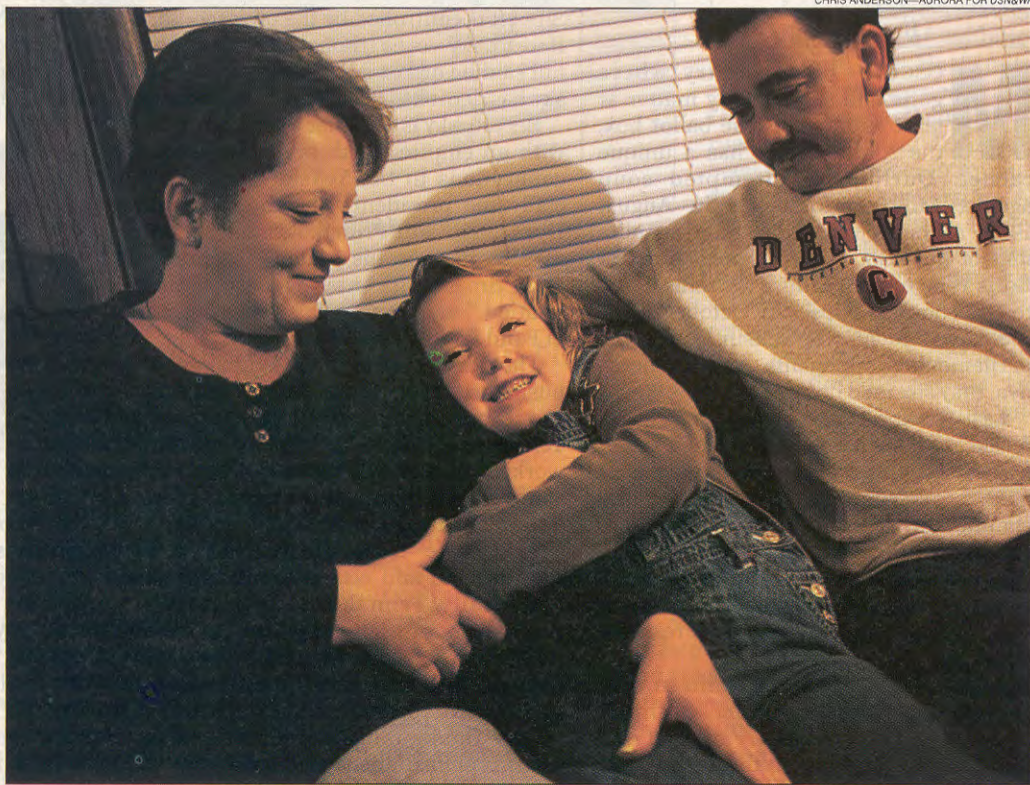
Company documents filed in connection with pending litigation tell a different story. During 1995 and 1996, while the label on Pondimin noted only four cases of pulmonary hypertension associated with



FENFLURAMINE AND  
PHENTERMINE

the drug, Wyeth received reports, mostly from Europe, of as many as 62 cases of the disease. Technically, the companies didn't have to tell the U.S. Food and Drug Administration about such "adverse events" from abroad because pulmonary hypertension was already mentioned as a possible side effect on

the drug's label. But the companies knew about more cases linked to the drugs. In their application to have Redux approved by the FDA, for instance, the companies noted 132 pulmonary hypertension cases linked to the drug. A Wyeth memo stated: "Now that a flow (stream? river?) of international serious reports has begun . . . we've been talking about reportability of them." Another memo listed 101 cases of



**PROGNOSIS.** Mary Perez, a former fen-phen user, at home in Arkansas with her daughter, Brittany, and husband, Thomas. Suffering from pulmonary hypertension, she is not expected to live another year.

pulmonary hypertension linked to Pondimin or Redux—on top of the previously reported 132 cases. Wyeth says it reported all domestic adverse events to the FDA and that the agency knew the drugs could cause pulmonary hypertension.

Despite the apparent problems, Wyeth and Interneuron pressed ahead. During negotiations with the FDA over the labeling of Redux, FDA officials proposed affixing a “black box” label, cautioning that some users could develop pulmonary hypertension. But according to a Wyeth official’s deposition, the company wanted to “avoid a public panic by implementing a black-box warning” that could hurt sales. The companies prevailed. A congratulatory Wyeth E-mail sent to the “SWAT Team” that conducted the negotiations with the regulators said: “The meeting with the FDA yesterday was a tremendous success! No black box!”

**Scribbles.** But even some Wyeth officials were divided over the safety issue. Joseph Sonk, director of the women’s health division, noted in an August 1996 memo that an in-house lawyer had wanted a much stronger warning on the Redux label. “SC strongly favors black box,” Sonk wrote, referring to attorney Sheila Connor. The note only surfaced last summer. Wyeth would not allow Connor to answer questions about the note in a deposition.

There was other evidence of concern by the companies. A “Standby Statement and Q and A for Wyeth-Ayerst Laboratories” was prepared as an informational aid for physicians prescribing Pondimin. In the margin of the document, a Wyeth attorney scribbled some notes. In the sentence, “Pondimin has been used safely and effectively . . .,” the attorney edited out the word *safely*. On another page, next to the word *safe*, the lawyer wrote, “Can’t say this” and “Don’t use the word safe or safely in an unqualified fashion.”

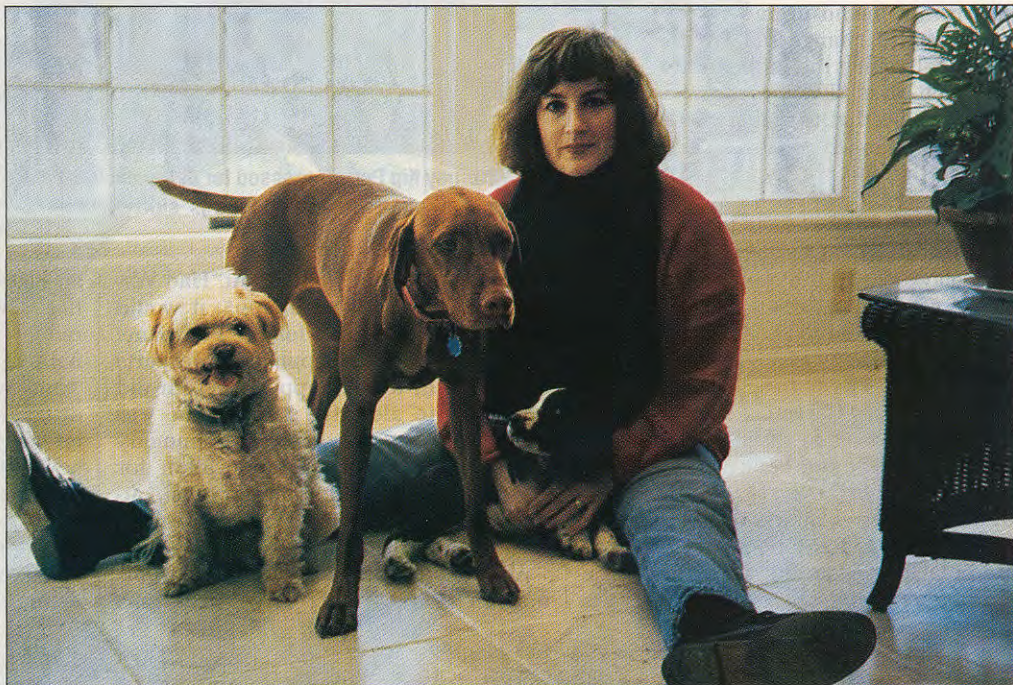
Mindful of the concerns about the drugs, Wyeth and Interneuron pressed the FDA. Interneuron turned to California Rep. Tom Lantos to try to close an FDA meeting about the drugs’ safety, prohibiting doctors and scientists from several health-advocacy groups from attending. A Lantos aide said his boss did not recall the meeting at the congressman’s office in February 1997. A review of political con-

tributions shows that officials of Interneuron, including its board chairman, CEO, and some of their wives, contributed to Lantos and his son-in-law, former Rep. Dick Swett, for whom Lantos was raising funds in 1996 and 1997.

The FDA yielded. It declined to press for the black-box warning and, in a highly unusual process, overrode the objections of FDA safety officers approving the use of Redux in 1996. But at the FDA, doctors

In fact, Interneuron’s plan to market Redux in the United States was a major element in a stock prospectus it was circulating on Wall Street in 1997. Wyeth, too, had a stake in winning FDA approval for Redux. Market analysts expected the companies to generate combined revenues of more than \$500 million a year from the sales of Pondimin and Redux in the United States.

Until now, the full fen-phen story has



**VICTIM.** Mary Linnen took the diet drugs for only three weeks before she quit, but the doctors who diagnosed her pulmonary hypertension couldn’t save her, and she died several months later.

were concerned about pulmonary hypertension. Some Interneuron executives were also troubled by the potential link. According to a March 1994 FDA memo, Interneuron Executive Vice President Bobby Sandage said in phone calls to the agency that the company had such concern about pulmonary hypertension that “it might be strong enough to consider withdrawing the NDA,” or new-drug application.

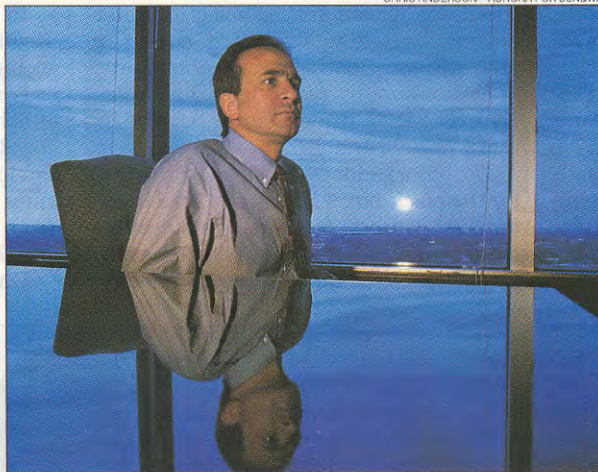
But Interneuron didn’t pull the application. In a later call, the memo says, Sandage told an FDA safety officer that the company had decided that “withdrawal, from a financial standpoint, was really out of the question because the company would be ruined.” A few months later, another FDA memo recorded that Sandage said Interneuron had “nothing to lose and would stop at nothing to get dexfenfluramine [Redux] approved.”



not been told. Wyeth has been quietly settling cases with plaintiffs related to pulmonary hypertension and heart-valve disease, often demanding confidentiality agreements. (Interneuron is currently trying to finalize a general settlement by itself.) But last year, two Dallas lawyers persuaded Wyeth’s and Interneuron’s attorneys to go forward with depositions and discovery. Kip Petroff and Robert Kisselburgh represent about 100 plaintiffs who have either pulmonary hypertension or heart-valve damage. The litigation has generated millions of documents. Among them: notes from Wyeth lawyers about how “safe” Pondimin was. Petroff was dumbfounded. “I was shocked. I mean, lawyers are always cautious, but if you can’t call your own drug safe, why are you pushing it?”

Central to the litigation pending against Wyeth and Interneuron are two

questions: What did the companies know, and when did they know it? Regarding pulmonary hypertension, Wyeth's former medical monitor, physician Frederick Wilson, testified in a deposition that he found company reports back in 1994 showing 37 confirmed Pondimin-related cases. Wilson wanted a new label to reflect the increase in reports of pulmonary hypertension, and he wrote a memo urging Wyeth executives to change the Pondimin label, which mentioned only four such cases. "Everyone agreed in June 1994 that the label needed to be changed," Wilson said. But Wyeth didn't change the label until June 1996—after Redux had been approved for sale by the FDA. Petroff asked the reason for the delay. Wilson professed not to know. "It seems like quite a long time," he said. A Post-it note found on the label change form dated May 1995 suggested one possible answer. The note, from Wyeth's top medical affairs director, Marc Deitch, said, "[we] need to discuss implication re: dexfenfluramine before proceeding." In a deposition taken two months ago, Deitch said the delay was due to the company's desire to have the Redux and Pondimin labels match. But according to the *Physicians' Desk Reference* of 1997, the



CHRIS ANDERSON—AURORA FOR USN&amp;WR

**ADVOCATE.** Attorney Kip Petroff pressed for details of what the companies knew about the two diet drugs' side effects.

two drugs' labeling is different. Had Wyeth changed the label in 1995, it would have raised a red flag for the FDA panel studying the Redux application, experts say, but that didn't happen. "Wyeth did not want to alert the FDA that it was seeing so many new cases of pulmonary hypertension while the application for Redux was still waiting for approval," attorney Petroff says. "It would have hurt the Redux application."

Wyeth and Interneuron also had information about heart-valve problems

among some users of the diet drugs, documents show. In the Redux approval application sent to the FDA, the companies reported several dozen cases mentioning heart-valve irregularities, according to FDA officials. Wyeth says the heart-valve references were not seen as a "signal" of a link between Redux and heart-valve disease. But "red flags should have gone up," says attorney Kisselburgh. Today, Wyeth officials are proffering new studies that they say show that alarms about the drugs were overstated. A company-funded study at Georgetown University said there was almost no link between their drug and heart damage. But that study was rejected by the *New England Journal of Medicine* last spring when it was submitted for publication. The editors insisted that the study be redone. "After they redid it," says the journal's deputy editor, Gregory Curfman, "there was a significant link between the drug and heart-valve irregularity." A senior official at the FDA says, "Most of these new studies from Wyeth only deal with short term exposure. . . . clearly, had the drugs stayed on the market longer, we would be seeing many more and more-serious cases of heart-valve damage and pulmonary hypertension." ■