Alzheimer's drug sharply criticized by medical experts

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Watching Alzheimer's disease steal away the memory, talents and very selves of its victims is hard enough for the people who love them. But a new pill formulated by a respected pharmaceutical company and approved by the Food and Drug Administration will do little to help most patients and bring misery to some, say two medical investigators.

The drug, Aricept 23 mg, is no more effective on the whole than the disappointing ones already on the market - but is more likely to cause gastrointestinal problems, wrote Drs. Steven Woloshin and Lisa Schwartz of Dartmouth Medical College in an article published Thursday in the medical journal BMJ.

The new formulation was devised to serve commercial objectives, they say, and was approved despite a poor showing in company-sponsored tests.

Woloshin and Schwartz described Aricept 23's march to market in 2010 as "perplexing" and "depressing" and wrote that "there is no excuse for manipulating vulnerable patients, desperate family members and their doctors to use a product that is most likely to cause net harm."

Dr. Marcia Angell, former editor of the New England Journal of Medicine and author of "The Truth About the Drug Companies," said the critique was important. "It illustrates very well how drug companies exaggerate the benefits of their drugs, minimize the side effects, and through misleading marketing to both doctors and the public convince

them that a new version of a drug, with a new patent, is better than the old one, whose patent has expired," Angell told the Los Angeles Times.

In 2010, the FDA and the pharmaceutical giant Eisai handed caregivers of those with Alzheimer's a new option for treating their loved ones - a 23-milligram dose of the long-available Alzheimer's drug donepezil, better known by its commercial name, Aricept.

Aricept 23 was aggressively marketed (Eisai's marketing partner in the United States is Pfizer Inc.) in magazine advertisements in a campaign that touted clinical benefits and plucked at caregivers' heartstrings.

But Schwartz and Woloshin say that the new option was a commercial plan to extend a brand-name medication's profit-making life by three years.

The practice, a common response to a drug company's imminent loss of patent rights on a product, is known as "evergreening." Aricept's patent rights were due to expire in November 2010, and generic drug manufacturers in short order were sure to market donepezil much more cheaply.

Pharmaceutical companies routinely look for ways - all perfectly legal - to extend the profit-making life of their product: They make a slight change to a drug's formula or dosage, or they combine it with another drug. With FDA approval, the new product is granted three years of legal protection from generic competition.

In the case of Aricept, developing a 23-milligram tablet created a dose that couldn't be reproduced by any combination of Aricept's existing 5- and 10-milligram pills, making the product new enough to win a three-year reprieve from low-cost competitors.

But Woloshin and Schwartz noted that Eisai's research showed that the pill offered a greater risk of side effects such as nausea and vomiting with no proof of benefit that a caregiver would be likely to notice.

FDA officials should not have allowed it, the authors said, because the clinical studies Eisai offered in support of its application did not meet standards the agency itself had laid out.

In a trial involving 1,400 patients with moderate to severe Alzheimer's, the 23-milligram dose of Aricept resulted in a small but statistically significant improvement in an index of overall cognition. But on a second measure, of "global functioning" - changes in behavior that a caregiver or physician is likely to notice - it failed to yield the improvements that the FDA had set as a condition of approval.

At the same time, subjects taking the 23-milligram dose, when compared with those taking 10 milligrams, reported significantly more nausea and vomiting - described by the director of the FDA's neurological drug division as "not trivial." In patients with dementia, nausea and vomiting can lead to pneumonia and death.

Dr. Lon Schneider, a University of Southern California Alzheimer's disease expert, said there had been widespread interest in whether a 23-milligram dose might help the minority of Alzheimer's patients taking two 10-milligram pills daily. Physicians, he said, hoped that one higher-dose pill would not only improve patients' dementia symptoms, but also release more slowly into the bloodstream, causing less stomach upset.

"It's fair to say the results of these studies were not positive and were not what we were all expecting," Schneider said.

Nonetheless, the FDA concluded that the 23-milligram dose of Aricept

would "very likely" improve a patient's overall functioning.

Marcia Diljak, a spokeswoman for Eisai, declined to comment on the BMJ article but noted that the FDA approved Aricept 23 mg for patients with moderate to severe Alzheimer's disease on June 23, 2010.

"So it's been on the market a long time," she said.

"The drug companies write the labels," and unless they make inaccurate claims, the FDA does not intervene, Woloshin said. But in the process, he added, many of the fine points of a drug's risks, benefits and uncertainties are not conveyed to consumers.

Medical ethicist Dr. Howard Brody of the University of Texas Medical Branch in Galveston said the Aricept 23 case is "a perfect storm" of commercial drive, regulatory failure and a patient base that is desperate, discouraged and vulnerable.

Because patients with Alzheimer's disease have good days and bad, caregivers would be powerless to counter the claims of Eisai that its new product is working better than its old product, Brody said.

Marina Del Rey, Calif., resident Mel Schwimmer, who cares for his 72-year-old wife, Barbara, was among those who jumped at the chance to see if she might respond to something new on the market.

He said he got her physician to write a prescription to replace her 10-milligram dose as soon as he heard about it. In a recent interview, Schwimmer said, "I wouldn't pass up the opportunity to try anything that comes out, in the hopes that it might be something that would slow the progress of this."

Barbara Schwimmer, diagnosed four years ago with Alzheimer's,

appears to be tolerating the new dose without signs of stomach upset, her husband said. But he is not sure how much it has helped.

"She seems to be doing well," he said. "But there's no scale I can measure other than my own observation. Even though she's doing well, there's some slippage."

The FDA needs to do a better job for consumers like the Schwimmers, Woloshin said, either by limiting the practice of "evergreening" or, at the very least, communicating what research has shown - and not shown - about the possible harms and benefits of a drug it approves.