Early in June 1998, Roche Laboratories of Nutley, NJ, abruptly and voluntarily withdrew its novel T-channel blocker, Posicor (mibefradil), from the market. The drug, used to treat hypertension, was just a few days short of celebrating its first year of release.

The withdrawal came after reports of dangerous and even fatal interactions with at least 25 other drugs, including common antibiotics, antihistamines, and cancer drugs. Posicor, which went onto the general market in August 1997 after its final approval in June of the same year, was being taken by almost 200,000 Americans and nearly double that number worldwide for both hypertension and angina. Its withdrawal was a logistical nightmare for many large cardiology practices faced with the need to notify patients that they would need to obtain a different prescription. In light of other recent withdrawals of medications from the market, the Posicor situation presented new questions about the perceived haste of the US Food and Drug Administration (FDA) to approve new medicines, a politically mandated speed-up that has drawn both praise and criticism.

Posicor is a novel antihypertensive that blocks both the T-type and L-type calcium channels, with greater selectivity for the T type. Also called mibefradil, it did not induce reflex tachycardia but slightly reduced the heart rate. In a talk paper released by the FDA, the agency said that Posicor reduces the activity of certain liver enzymes that are important in helping the body eliminate many other drugs.

Posicor inhibits cytochrome P450 2D6 and 3A4 and could interact by increasing the plasma concentrations of concomitantly administered drugs. At times, the FDA wrote, this increased accumulation of drugs reached dangerous levels in the body.

Interactions, particularly with those drugs that also affect liver metabolism, appeared to cause catabolism of important abdominal muscles in a few people. The interaction was considered extremely dangerous.

Posicor has had a troubled history. When it was released, Roche warned that it could not be used in combination with 3 specific drugs: astemizole, cisapride, and terfenadine. But quickly, it appeared that the interaction problem had been underestimated. In December 1997, the FDA strengthened the labeling, adding lovastatin and simvastatin as 2 drugs that should never be administered with Posicor. By the time Posicor was withdrawn, more than 25 drugs had been determined to be potentially dangerous when used with Posicor. The FDA noted that the number of drugs “cannot be practically addressed by standard label warnings.”

The agency further stated that “since Posicor has not been shown to offer special benefits (such as treating patients who do not respond to other anti-hypertensive and antianginal drugs), the drug’s problems are viewed as an unreasonable risk to consumers.”

Both the company and the FDA warned that patients should not discontinue Posicor on their own. They were advised to contact their physicians for appropriate alternative therapy. Those taking Posicor were told not to add any new medication to their current medications without consulting their physicians.

But by mid-June 1998, it had become clear that the drug’s problems were not over. In an unusual move, the Journal of the American Medical Association allowed the premature release of information scheduled for its July 8, 1998, issue about the dangers posed by switching patients from Posicor to other calcium channel blockers such as felodipine and timolol. In his report, Michael E. Mullins, MD, of the Oregon Health Sciences University outlined the cases of 4 patients who had gone into shock within 12 hours of the drug switch.

Mullins wrote that 1 of the patients died, but the other 3 recovered after treatment in the emergency department and intensive care unit. Patients ranged in age from 55 to 79 years and were taking from 50 to 100 mg of Posicor daily along with drugs to treat other conditions. Their doctors switched them from the drug before it was withdrawn because it was not working as well as was wanted.

Mullins said it can take many days for Posicor to leave the patient’s system, and he recommended a 7-day period between ending Posicor and beginning other calcium channel blockers or β-blockers. Felodipine and timolol require a 14-day waiting period.

The question of why such interactions did not show up in earlier testing is not easily answered. In response to questions, Roche officials said, “All known adverse effects seen in clinical trials were reported to the FDA as part of the original NDA [New Drug Application] for Posicor, and all appropriate data regarding drug interactions were included in the product’s PI [package insert] at the time of approval. As a result of widespread clinical use, it was determined that the combination of Posicor and some other commonly used drugs may increase the side effects of these other medications. This information was not evident during clinical trials and was immediately communicated to the FDA in full compliance with the agency’s established reporting system. As a result, Posicor’s labeling was revised in December 1997.

“Roche has worked closely with the FDA since the product was launched and has made appropriate labeling changes in conjunction with developing knowledge gained through regular post-marketing surveillance about drug interaction profiles and pharmacokinetic/pharmacodynamic interactions.”

In the beginning, the company warned that Posicor should not be prescribed for patients with severe hepatic impairment.
It conducted several clinical trials to demonstrate the drug’s antihypertensive effect, including 4 placebo-controlled, double-blind, randomized trials conducted for 4 to 14 weeks in patients receiving no other treatment and 1 trial in patients receiving 25 mg of hydrochlorothiazide for blood pressure control. These trials involved 933 patients receiving Posicor and 190 receiving placebo. Once daily administration of 50 and 100 mg of Posicor was consistently associated with clinically and statistically significant reductions in both systolic and diastolic blood pressure. Posicor was also combined with diuretics, ACE inhibitors, and β-blockers to determine if it had additive antihypertensive effects.

Roche withdrew the drug from the market because of interactions, but the company denies that there is a causal link between administration of Posicor and any deaths reported to the FDA. “Given the patient population and the nature of the underlying disease being treated, this population is at risk for such events, which have been reported,” the company said in a released statement. “No causal link has been established between Posicor and reports of death.”

Craig Pratt, MD, a professor at Baylor College of Medicine in Houston, Tex, has served on FDA advisory committees that approve such drugs and as advisors to companies such as Roche. He thinks the case of Posicor is a good argument for aggressive postmarket surveillance of drugs that have received approval. “It is inevitable that there are some reactions or untoward effects that will crop up in clinical practice that were not shown in the original phase III protocols,” he said. “Some things are rare. Protocols [used in phase III trials] are done at universities or in practices that are used to doing protocols. The protocol is adhered to closely, the physicians read the indications and contraindications.”

In the case of Posicor, he said the PIs had 2 lists of relative contraindications and cautions that specifically listed all categories and drugs that turned out to be problems. But once a drug is on the market, it is often used “off label,” he said. “It’s used for purposes and in patients for whom the drug was not intended or for whom it was contraindicated. The sum of all those things explains the difference between what’s noted in clinical trials and what’s noted in the community.”

Even though companies like Roche spend millions of dollars getting such drugs to market, if the drug is not the only one that works for a certain indication and has too many problems, it is not unusual for the company to withdraw it from the market, said Pratt. “Sooner or later, the practical issue is to get rid of it.”

The issue in such drugs is not that 20,000 more people should be included in clinical trials, he said, but rather that “we should follow the first 20,000 patients for a year in the community.” That will require some special incentives to physicians. “If you wait for the doctors to report, it will be woefully inadequate, and if it’s a weird side effect, they might not connect it to the drugs,” said Pratt.

But, he said, if there is an incentive such as a discount on the drug to patients who fill out a postmarketing form, then such effects might come to the attention of the FDA sooner. “Some kind of partnership with the pharmaceutical companies seems to be mandatory.”

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Withdrawal of Posicor From Market
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Circulation. 1998;98:831-832
doi: 10.1161/01.CIR.98.9.831
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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