

phase I PACE trial (median treatment 2.7 years) experiencing such events.

In an analysis of the phase II study, performed in November 2012 with a median follow-up of 15 months and published in the *New England Journal of Medicine*, researchers initially reported a 7.6% rate of patients with serious adverse arterial thrombosis events [N Engl J Med 2013;369:1783–96]. That rate prompted a boxed warning for these side effects when the drug was approved. After the overall rate of serious adverse vascular events rose in subsequent months, Ariad suspended the PACE trial and terminated the phase III EPIC trial, a first-line randomized trial of ponatinib versus imatinib.

The FDA says it will continue to evaluate ponatinib in order to determine whether the benefits may outweigh the risks for some patient populations. Patients enrolled in the trial who benefited from ponatinib may continue treatment under an emergency Investigational New Drug application filed by their physician.

“We know that cardiovascular risk is an evolving problem with cancer patients as you deal with problematic populations who have been previously treated,” says Christopher-Paul Milne, DVM, MPH, JD, director of research at the Tufts Center for the Study of Drug Development in Boston, MA. “Whatever underlying cardiovascular risk there was may be increased with second- and third-line agents.”

Despite the significant risk of adverse events with ponatinib, suspension might have been avoided under a better system for monitoring and reporting adverse events, says Javid Moslehi, MD, codirector of the cardio-oncology program at Dana-Farber Cancer Institute in Boston.

“Currently, National Cancer Institute criteria for reporting adverse events with cancer drugs are different than ones used for other classes of drugs such as cardiovascular drugs, compromising the detection of cardiotoxicity,” says Moslehi, who coauthored a perspective on the PACE study findings [N Engl J Med 2013;369:1779–81].

“If we know the root of the problem we can address it,” he says. “It could be because of rapidly progressing atherosclerosis, and it could be very helpful if you treat those patients with a statin.”

Similarly, patients with arterial clots might be pretreated with aspirin or the blood clot preventer Plavix (clopidogrel; Bristol-Myers Squibb and Sanofi), and those with vasospasm could be started on nitrates to open up the artery.

The suspension of ponatinib also raises questions about whether the accelerated approval process exposes patients to excessive risk. However, it appears as if the process worked well in this case, says Milne.

“This issue only came to the FDA’s attention a few weeks ago, and they acted on it quickly,” he says. “It shows that they are increasing the ways they can make decisions in the post-marketing scenario.” ■

## Strategic Plan Aims to Curb Drug Shortages

The U.S. Food and Drug Administration (FDA) has released a strategic plan to strengthen its response to imminent and existing drug shortages, as well as a proposed rule requiring manufacturers of drugs and biologics to alert the agency to the impending discontinuation of any products or interruptions in manufacturing that could deplete supply.

The “Strategic Plan for Preventing and Mitigating Drug Shortages,” released on October 31, explains that early notification of manufacturing disruptions gives the FDA time to work with drug companies to help resolve such disruptions, identify other companies that might be able to increase production, and expedite inspections and reviews of product submissions from drugmakers that might help prevent or ease shortages.

The plan also calls for incentives for manufacturers to improve the quality of their drugs and facilities.

“The FDA can only do so much,” says Erin Fox, PharmD, director of the drug information service at University of Utah Health Care in Salt Lake City. “We know that many of the ongoing problems are related to poor manufacturing quality and companies not investing in their factories over time.”

One manufacturer, Ben Venue Laboratories in Bedford, OH, announced in October that it would permanently cease all drug production by the end of

2013. The company had halted production and spent more than \$350 million since 2010 to repair and upgrade its facilities, but declared that the ongoing investment needed to overcome its challenges is too great for it to continue.

“That took away some of the hope that some of the shortages are going to be resolved quickly,” says Fox. She notes that Ben Venue was the only U.S. manufacturer of thiotepa, which is used to treat ovarian, breast, and bladder cancers and lymphomas. For now, the FDA is allowing an imported replacement, the brand-name drug Tepadina from Italian drugmaker Adienne, although the logistics of purchasing it further complicate the situation.

The proposed rule, released on the same day as the strategic plan, implements the early notification requirements included in the 2012 Food and Drug Administration Safety and Innovation Act. It requires manufacturers to alert the agency about potential drug shortages at least 6 months prior to permanently discontinuing a drug or interrupting its production. If that isn’t possible, manufacturers should do so “as soon as practicable” but no later than 5 days after the disruption. The proposed rule also spells out the types of products covered and the information to be reported.

Unlike an interim rule currently in force, the proposed rule would extend to manufacturers of biologic products, such as monoclonal antibody products and vaccines.

Janis Abkowitz, MD, president of the American Society of Hematology, applauded the inclusion of both drugs and biologics in the proposed rule. Shortages, she says, have been particularly troublesome for hematologists because “many of the drugs most vulnerable to shortages—older, generic sterile injectables—are used to treat blood disorders,” including cancer.

Early alerts about possible disruptions in drug supplies since 2011 have helped prevent some shortages. In 2012, shortages of more than 280 drugs were averted, and reports of new shortages dropped to 117, from 250 the previous year.

At the end of September, says Fox, 294 drugs were in short supply, 31 of which were cancer drugs. ■