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FDA Panel Seeks Tougher Antibiotic Labels

Mounting evidence of previously unknown, and sometimes permanent, side effects prompted review

By **THOMAS M. BURTON**
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SILVER SPRING, Md.—A Food and Drug Administration advisory panel overwhelmingly called for heightened label warnings on widely prescribed antibiotics called fluoroquinolones because of unusual but sometimes devastating side effects.

The action followed a day of emotional testimony from dozens of patients who said these drugs have had a wide range of harmful effects on their health and cognitive ability.

The agency decided earlier this year to have its advisory committee examine the class of antibiotics because of mounting evidence of previously unknown, and sometimes permanent, side effects.

Panel member Dr. Tobias Gerhard, professor in the Department of Pharmacy Practice at Rutgers University, said the panel voted for the stronger label warnings "because of the remarkable testimony that we have heard today."

The drugs are commonly prescribed, with a total of more than 36 million prescriptions issued in 2014, according to drug-research firm IMS Health. The panel was examining the drugs for their safety when

used to treat sinus infections, urinary-tract infections and bronchitis that worsens existing chronic obstructive pulmonary disease.

The panel was asked to consider whether the current labels adequately explain the benefits and risks for the three conditions and, if not, whether the labels should be revised. The vote for revising labels was 21-0 on sinusitis; 18-2, with one abstention, on bronchitis; and 20-1 regarding urinary-tract infections.

The FDA doesn't have to follow advisory panels' recommendations, but it often does so. The panel didn't recommend specific warning language; that would be decided by the agency itself.

Most fluoroquinolones now are sold as generic drugs, but the well-known brand names include Bayer AG 's Cipro, generically called ciprofloxacin; and Johnson & Johnson 's Levaquin, or levofloxacin. This class of powerful antibiotics has been available for nearly three decades.

During Thursday's testimony, one witness, 59-year-old Andrea Siani of Boston, said she had been in perfect health when she took Levaquin in March 2014 to treat non-life-threatening pneumonia.

As a result, "all my tendons were damaged," she told the panel. "Nine pills took my health away. I suffered excruciating pain over a year." Since then, Ms. Siani, director of a social-services program, said she walks with crutches.

In recent years, the FDA and some outside drug-safety doctors have been accumulating evidence on a variety of serious safety issues with this class of drugs. These range from cardiac rhythm disturbances, to movement impairment called peripheral neuropathy, to cognitive problems such as difficulties concentrating.

Doctors representing companies responded at Thursday's hearing that this class of drugs is especially important to treat serious infections, such as cases of bronchitis that have worsened patients' chronic obstructive pulmonary disease. They said the drugs are vital to alleviate severe COPD, which can be fatal.

Dr. Jeff Alder of Bayer said the class of drugs have "a proven role for treatment" of several infections.

Bayer said its fluoroquinolones, Cipro and Avelox, "have been used to treat a range of infections for many years...It is important for physicians to have access to multiple options, including Cipro and Avelox, for treating bacterial infections that, if left untreated, may cause serious complications."

In a statement, Johnson & Johnson said Levaquin has been used for

nearly 20 years to treat life-threatening and other infections. The company continues "to support the safe and appropriate use" of fluoroquinolones.

As early as April 17, 2013, the FDA's Office of Surveillance and Epidemiology, which evaluates drug safety, concluded: "We continue to find an association between fluoroquinolone antibiotic use and disabling peripheral neuropathy."

These cases included weakness, numbness, pain, discomfort, burning and tingling. That office also reported the case of a man who had a hypersensitivity reaction while taking Levaquin. After getting a second treatment with the drug, he was admitted to the intensive care unit and died within two weeks, according to FDA documents.

The agency issued a public warning about these concerns in August 2013, but it has since concluded that a constellation of seemingly unrelated problems can occur in a small number of patients taking a fluoroquinolone antibiotic.

In a more recent review, FDA staff reported that this class of drugs carries a risk of cardiovascular disease, and of tendon rupture and peripheral neuropathy.

"Over the life-cycle of these drugs, several adverse reactions have been reported and most of them were not evident in the preapproval safety databases," the FDA reviewers wrote.

Charles L. Bennett, a drug-safety specialist at the University of South Carolina, said that putting this range of bad reactions into a black-box warning on the drugs' labels would have a "significant positive impact." It would, said Dr. Bennett, clearly inform doctors and patients of "serious, sometimes permanent damage to multiple body systems."

Write to Thomas M. Burton at tom.burton@wsj.com