TRENDS-in-MEDICINE

BULLETIN:

FDA APPROVES FIRST BIOSIMILAR

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by Lynne Peterson

Four years to the month after President Obama signed into law the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), passed as part of the Affordable Care Act, the FDA approved the first biosimilar, Novartis/Sandoz's Zarxio (filgrastim-sndz), a biosimilar of Amgen's Neupogen (filgrastim), under the 351(k) pathway, for all the uses for which Neupogen is approved:

- cancer patients receiving myelosuppressive chemotherapy.
- acute myeloid leukemia (AML) patients receiving induction or consolidation chemotherapy.
- cancer patients undergoing bone marrow transplantation.
- patients undergoing autologous peripheral blood progenitor cell collection and therapy.
- patients with severe chronic neutropenia.

FDA officials explained that a biosimilar product (or an interchangeable product) must have the same mechanism(s) of action, route of administration, dosage form, and strength as the reference (brand) product, and can only be approved for condition(s) of use that have been previously approved for the reference product. In addition, the biosimilar must meet the Agency's manufacturing standards.

In a memo to FDA staff, Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER), said, "The approval of Zarxio is quite significant as it paves the way for the future of biosimilar approvals. A successful biosimilars review process will spark the development of a new segment of the biotechnology industry in the United States. It will also provide significant benefits for patients, making available more affordable treatments that clinicians will be assured are safe, effective, and of high-quality."

However, Zarxio was approved only as a **biosimilar**, ***not as interchangeable*** with Neupogen. This means Zarxio cannot be automatically substituted by pharmacies for Neupogen. But, depending on state laws, pharmacists can call doctors and ask them if they want to give the patient Zarxio instead of Neupogen (and vice versa).

In a teleconference with reporters, John Jenkins, MD, director of the FDA's Office of New Drugs, CDER, said Sandoz did not request approval of Zarxio as an interchangeable product. Leah Christl, PhD, associate director for therapeutic biologics in the FDA's Office of New Drugs, CDER, said that interchangeable products have an additional hurdle: they must also provide data and information to demonstrate that the product is expected to produce the same clinical results in a patient, and, for a product to be administered more than once, that the safety and efficacy is not impacted by alternating between it and the reference product."

Dr. Jenkins added, "We would have to be comfortable that switching [back and forth between the biosimilar and the brand/reference product] would not introduce any greater concerns for the patient…One issue in switching might be development of drug-

specific antibodies to the biological drug that may interfere with safety or efficacy. That would be one thing we would look at with an interchangeable product…We have not yet issued guidance on interchangeability."

What does this mean at the pharmacy level? Dr. Jenkins added, "The FDA did not determine it could be changed at the pharmacy level without the intervention of the healthcare provider." Dr. Christl said, "The practice of pharmacy-level substitution is driven by state laws and overseen by state boards of pharmacy…Calling [a healthcare provider] is not substitution…Substitution is without the intervention of the healthcare provider…For these, the pharmacist could always call the provider and talk about whether a different product than written is appropriate, but that is not what we call substitution."

The bottom line is that the only difference between Neupogen and Zarxio is likely to be price. Dr. Jenkins said, "We did not see any differences that suggest there should be any situations where a prescriber would have to choose one or the other. They should perform the same…When competition comes into the marketplace, it often results in lower prices. Biologics tend to have very high prices, and with competition one of the goals is, hopefully, to see lower prices to make access better for patients who need these products."

FDA officials insisted that the generic (non-proprietary) name of this biosimilar is not a precedent for how it – or other biosimilars – will be named in the future. Rather, the FDA called the generic name a "placeholder non-proprietary name."

This approval came before the FDA had issued guidance on a number of biosimilar issues, including naming, interchangeability, and labeling. Dr. Jenkins said the Agency hopes to issue naming guidance "soon." Dr. Christl said labeling guidance is on CDER's agenda this year.

Interestingly, the Zarxio label does not include any of the biosimilarity data that Sandoz submitted to the FDA. Dr. Christl basically said those data are not necessary for healthcare providers to make appropriate decisions. Dr. Jenkins added, "Not all data to support biosimilarity will be in the label because those data are not necessary for the physician to prescribe the product."

When can Sandoz launch Zarxio? Dr. Jenkins said the company can launch it as soon as it wants, "They have a trade name, a proprietary name, and an approved label, so from the FDA standpoint, they can launch and market whenever they make that decision."

The FDA currently is reviewing at least four other biosimilars filed under the 351(k) pathway – at least that is how many filings have been publicly disclosed by companies. Dr. Jenkins said the review time for these products is 10 months, and there is no priority review or fast track. As with NDAs, time extensions are always a possibility if there are major amendments. For a while, most are likely to be taken to an advisory committee before approval, particularly if it is a first biosimilar of a reference product.