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FDA Makes Opioid Labeling Changes, Requires More Postmarketing Data; REMS Next

The FDA has modified the safety labeling for extended-release (ER) and long-acting (LA) opioid analgesics, as well as required further postmarketing studies to be conducted by the manufacturers of the agents. Although many of the changes reflect requests made in a petition from a physicians' group looking to limit the prescribing and use of opioids for safety reasons, many of the group's recommendations were not adopted by the FDA.

The drug labeling sections that are affected include Dosage and Administration, Warnings and Precautions, Drug Interactions, Use in Specific Populations and Patient Counseling Information, as well as the Medication Guide.

"The labeling changes demonstrate the FDA's resolve to reduce the serious risks of long-acting and extended-release opioids while still seeking to preserve appropriate access for those patients who rely on these medications to manage their pain," FDA Commissioner Margaret A. Hamburg, MD, said in a statement.

According to Douglas Throckmorton, MD, deputy director for regulatory programs in the FDA's Center for Drug Evaluation and Research, the new labels "describe more clearly the risks and safety concerns associated with ER/LA opioids and will encourage better, more appropriate prescribing, monitoring and patient counseling practices involving these drugs."

Chief among the Physicians for Responsible Opioid Prescribing's (PROP) requests that were included in the new labeling is language stating that opioids should not be prescribed for moderate pain. The updated labeling states that ER/LA opioids are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

In a press statement on its website, the FDA stressed the need for individualized treatment for chronic pain patients, and that the new labeling is designed to help health care professionals reach these goals with each of their patients.

"The updated indication further clarifies that, because of the risks of addiction, abuse and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief," wrote the FDA in the statement.

Lynn Webster, MD, president of the American Academy of Pain Medicine, said the reworked

indication from moderate to severe pain to pain "severe enough to warrant opioids is more appropriate, as it will take into account factors other than a pain scale score that should be considered when prescribing opioids."

Neonatal Warning

Another major addition to the labeling is the inclusion of a boxed warning on the risk for neonatal opioid withdrawal syndrome, associated with chronic use during pregnancy.

Dr. Webster praised the FDA's inclusion of a boxed warning on neonatal opioid withdrawal syndrome, but used the labeling change announcement as an opportunity to point out a common misconception.

"An important positive development was adding a boxed warning that babies born to mothers on opioids may experience opioid withdrawal," he said. "However, it should be noted that the media has often mischaracterized the withdrawal as a sign the babies are addicted. This is not correct. Babies become physically dependent through their mothers and have to be treated for withdrawal like adults who experience withdrawal. Of course, this is very stressful and a miserable experience for an infant."

PROP Requests Left on Table

Andrew Kolodny, MD, president of PROP, tempered his happiness about the labeling changes with frustration regarding changes that were not made.

"We [PROP] were pleased, but we feel that FDA should have gone much further," he said. "Their decision to exclude IR opioids is baffling, because all the risks are the same.

"We're disappointed that they didn't add a suggested maximum duration of use of 90 days and a maximum dosage of 100 mg morphine equivalents. We wanted use beyond these parameters to remain an option for physicians and patients, but we wanted it to be off-label because risks of long-term and high-dose use are likely to outweigh benefits for most chronic pain patients."

Dr. Webster said the labeling changes marked "a good day for people in pain who find opioids helpful.

"The FDA did a careful and thoughtful review of the petition presented by Physicians for Responsible Opioid Prescribing and decided there was not enough evidence to support most of the arguments made in the petition," he said.

More Research, Changes to REMS

In addition to the labeling changes, the FDA announced new postmarketing clinical study requirements focusing on "the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death." Dr. Webster described the FDA's requirement for manufacturers of opioids to conduct long-term safety and efficacy studies as "long overdue."

After final labeling is in place, the FDA intends to revisit the ER/LA opioid analgesics' Risk Evaluation and Mitigation Strategies (REMS) program that was approved in 2012, "to reflect the updated information." The current REMS mandates that the manufacturers of ER and LA

opioid analgesics provide training for health care professionals who prescribe these agents, as well as educational materials for the health care professionals and for their patients that explain how to safely use the medications.

—Donald M. Pizzi