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Quick Pulse

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FDA Issues Second Safety Warning for Fentanyl Transdermal Patch

The FDA issued its second safety warning about the fentanyl transdermal system, an adhesive patch, and asked manufacturers of all fentanyl patches to update their product information and develop a medication guide. The agency issued a similar warning in July 2005, saying that the directions on the product label and on the patient package insert should be followed exactly in order to avoid overdose.

The FDA said that it issued the warning because it has continued to receive reports of deaths and life-threatening side effects after doctors have inappropriately prescribed the patch or patients have incorrectly used it. The patch is marketed under the brand name Duragesic by Johnson & Johnson, and generic versions of the product are sold by other manufacturers. All versions of the product and all doses are affected.

Recent reports to the FDA describe deaths and life-threatening side effects after doctors and other healthcare professionals inappropriately prescribed the patch to relieve pain after surgery, for headaches, or for occasional or mild pain in patients who were not opioid tolerant. In other cases, patients used the patch incorrectly, replacing it more frequently than directed in the instructions, applying more patches than prescribed, or applying heat to the patch – all resulting in dangerously high fentanyl levels in the blood.

Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products said, "The history here is important. We did this two years ago…Unfortunately, we still do see cases of patients using the product incorrectly and prescribers prescribing the product incorrectly, and some of these cases have resulted in life-threatening events and some even in death."

The FDA approved the first fentanyl patch in 1990 for patients with persistent moderate-to-severe pain who have become opioid tolerant. The patch is most often prescribed for patients with cancer. Dr. Rappaport said that all four generic products and all doses are included in the warning, "Even the lowest doses of these patches can cause fatal respiratory depression in an opiate non-tolerant patient."

Asked about the specific numbers of deaths, Dr. Rappaport said, "I want to focus on the individual cases and not how many cases there are. I know there is some interest in how many cases we've had reported since 2005, and we're working to get you those numbers. But the more important issue is that it's not a large number of cases…That's not the reason we're coming out with this safety communication at this time. There are a small number of cases that are very concerning because they are preventable, and that's why we're (issuing the new warning)."

There have been some unofficial reports of up to 3,500 patients who have died wearing the patches, but Dr. Rappaport declined to give numbers on patch-related deaths, "These drugs are used in patients who have chronic painful conditions from serious disease. Fentanyl patches are used in great numbers in terminal cancer patients in hospices, and it's not surprising that many of the patients who die are going to die with a Duragesic patch on. That's the nature of treating pain in terminal disease, and it's not surprising at all…Adverse event reports are notoriously hard to tease out. They come from prescribers, nurses, patients, families. Anyone can send an adverse event report to the Agency."

Dr. Rappaport said fentanyl patches, which contain the opioid fentanyl, a potent narcotic, are supposed to be prescribed only for patients who are already tolerant of opiate drug products, "In some cases prescribers are giving these patches to patients who are not opioid tolerant and may give them post-surgery or for mild pain, and we've even seen cases (where they've been given) for headache. And in those patients, (the patches) can cause serious and life-threatening respiratory depression. We're also still seeing cases of patients not using the products correctly."

Prescribers must inform patients and educate patients about the dangers of using them in certain ways. Dr. Rappaport said, "They cannot be used in a setting where they'd be exposed to heat, such as a heating pad or a hot tub or a heated water bed, that increases the amount of drug that's absorbed from the patch. There are a number of other settings in which the drug has to be properly used such as when a patch falls off and needs to be replaced. There are detailed instructions for how and when to replace that patch. So, all of these types of aspects of using the fentanyl patches are essential for both the prescriber and patient to understand."

Asked what makes the FDA think that a second warning will prevent misuse, Dr. Rappaport said, "We have to be hopeful it will because we don't have a lot of other means to address this problem. Many patients out there have chronic painful conditions and can't tolerate oral medications for one reason or another. These are useful products for that patient population, so we want to make sure they remain available for those patients."

Dr. Rappaport said that the problems are seen only with the patches and not with other forms of fentanyl, "This is unique to patches. The other formulations are used in a different way. They (the other formulations) have risks associated with them, but not the same risk. It's unique to patches because of the pharmacokinetics – the way the drug is delivered to the body and the way it's metabolized. That's complicated by the patch formulation."

Asked why doctors aren't getting the word about potential dangers of misuse, Dr. Rappaport said, "I believe the company (J&J) is making efforts to do that. I think that the problem is these days there are a lot of patients out there. The number of patients with chronic pain in this country is enormous, and there aren't enough trained physicians to treat them. A lot of primary care physicians are not experienced with using Duragesic and inadvertently cause these problems, and that's why we're attempting to reach out to them."

Asked which patients get the patch, Dr. Rappaport said, "Sometimes it's just that the patch is a convenient dosage form, so often patients are switched from oral or IV to a patch, and they can leave it on for three days. And there are patients who have trouble swallowing and tolerating oral medications as well. So, the patch does have some advantages."

Asked about the number of problems with the patches due to misuse or mis-prescribing, Dr. Rappaport said, "It's difficult to give you an exact number. If you're going to talk about which cases are caused by mis-prescribing and by misusing – you have a cancer population on these drugs – the numbers of deaths that occur on the fentanyl patch is in the hundreds, but the cause of death by mis-prescribing or misuse is much smaller."

The Institute for Safe Medication Practices (ISMP) reportedly is asking for a limited prescribing program. *Why didn't the FDA take its warning a step further?* Dr. Rappaport explained, "We were grateful to the ISMP for alerting us back in the summer, but that particular reform is really not a feasible one in this country, and that goes back to how pain patients are treated. The estimates are there are up to 60 million chronic pain patients in this country, and they're treated by 4,000 pain specialists in the country. The rest are treated by family practice, local neurologists, internists – all of whom need access to these drugs. The last thing we want to do is limit the availability of good analgesics to chronic pain patients. If anything, we have undertreatment of chronic pain patients in this country."

Asked about patch abuse, he said, "There is abuse of the patches as there is with all opiate products; we do see that, but that's not what this safety communication is about today." As for reports of using the patch for headache, he said, "I can't give an exact number, but I know of at least one case of the product being used for headache, with our post-marketing reporting system, we see about 10% of the actual reports, so it's likely to be considerably higher than that."

In its Public Health Advisory and Healthcare Professional Sheet, the FDA stressed the following safety information:

- **Appropriate patients.** Fentanyl patches are only for patients who are opioid tolerant and have chronic pain that is not well controlled with other pain medicines. The patches are not to be used to treat sudden, occasional, or mild pain or pain after surgery.
- **Signs of overdose.** Healthcare professionals who prescribe the fentanyl patch and patients who use it should be aware of the signs of fentanyl overdose: trouble breathing or slow or shallow breathing; slow heartbeat; severe

sleepiness; cold, clammy skin; trouble walking or talking; or feeling faint, dizzy, or confused. If these signs occur, patients should get medical attention right away.

- **Other medications.** Patients prescribed the fentanyl patch should tell their doctor, pharmacist, and other healthcare professionals about all the medicines that they take. Some medicines may interact with fentanyl, causing dangerously high fentanyl levels in the blood and life-threatening breathing problems.
- **Proper use.** Patients and their caregivers should be told how to use fentanyl patches. This important information, including instructions on how often to apply the patch, reapplying a patch that has fallen off, replacing a patch, and disposing of the patch, is provided in the patient information that comes with the fentanyl patch.
- **Heat.** Heat may increase the amount of fentanyl that reaches the blood and can cause life-threatening breathing problems and death. Patients should not use heat sources such as heating pads, electric blankets, saunas, or heated waterbeds or take hot baths or sunbathe while wearing a patch. A patient or caregiver should call the patient's doctor right away if the patient has a temperature higher than 102 degrees while wearing a patch.

The FDA is working with manufacturers to continue to add more warnings and cautions in the label and more instructions for the proper use of these products. Dr. Rappaport said, "We did feel it was necessary to make a public safety statement, and we're hoping to get this message out to the patients and prescribers."

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