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Quick Pulse

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FDA Imposing New Risk Management Program on Many Opioids

Citing an increase in the misuse, abuse, and unintentional deaths from some extended-release pain medications, the FDA said that it is taking sweeping steps to force 16 manufacturers of two dozen drugs to comply with a new risk evaluation and mitigation strategy (REMS). Opioid drugs formulated in extended-release versions of OxyContin, morphine, and fentanyl patches will be affected.

There will be no immediate changes, and no action is expected until at least fall of this year. Pain medications that are immediate-release will not be affected. For drugs that are affected, labeling changes will be likely, and the FDA hinted that the REMS could be similar to an existing program, iPLEDGE, designed to limit the use of Roche's Accutane (isotretinoin) by women of child-bearing age because of potential birth defects. That program requires doctors, pharmacists, and patients to register and meet certain requirements in order to write, fill, or acquire prescriptions.

On February 6, 2009, the FDA sent letters to 16 manufacturers of the 24 medications, including Purdue Pharma, which makes OxyContin (oxycodone); Johnson & Johnson, which makes Duragesic (a fentanyl patch); and King Pharmaceuticals, which makes Avinza (an extended-release morphine). The FDA said that it plans to meet with these manufacturers on March 3, 2009, to begin developing the REMS. The FDA will also meet with other federal agencies, including the Drug Enforcement Agency, patient and consumer groups, and doctors to get input on the plan. A public meeting will be scheduled for late spring or early summer 2009 before the FDA hammers out the final plan. Dr. John Jenkins, director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research (CDER), said, "After the public meeting, we will take the information and digest it, and then we will let the sponsors know exactly what we expect to be included in the REMS, and it will take some time after that to work with the companies to get this program up in place. This will be a complex undertaking so it will take some time."

The FDA said that it is taking this action because of the Agency's continuing concern about unsafe use of narcotic pain relievers, brand name and generic. The FDA has the authority to develop REMS under legislation that took effect last year which gives the Agency new power to mandate risk management programs.

Dr. Jenkins said, "We recognize that this is going to be a relatively massive new program…(It's) an order of magnitude greater than the other programs that we have now, like the isotretinoin program. It's likely that legitimate patients will see new procedures that will be in place for obtaining these products, but we hope to make them not so intrusive that it impacts on their ability to receive the products, while at the same time meeting the second goal…of safe use. We would like to be

effective in substantially reducing the death and other adverse events that are reported because of thse products."

Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, said that new data from the Substance Abuse and Mental Health Services Administration (SAMHSA) showed that misuse of prescription pain killers continues to increase, "Overall 5.2 million people 12 and older reported using prescription pain relievers 'non-medically in the past month' in 2007, and of particular concern was that the numbers seem to be increasing in certain age categories. Use among adults 26 and older increased from 1.3% to 1.6%, so this is an ongoing problem that's getting worse."

Dr. Jenkins said that millions of Americans take these drugs, "The use of these products is quite extensive. 2007 data suggest approximately 21 million prescriptions were dispensed for the 24 affected products, representing 3.7 million unique patients, so this is a very extensively used group of medications. As far as the risk, it's hard to get exact numbers and to sort out the numbers exactly for the cause of the serious adverse events, but there are hundreds of deaths reported each year for these products related to misuse, which could be intentional and unintentional abuse and death…Opioid drugs have benefit when used properly and are a necessary part of pain management for certain patients, but at the same time they have serious risks when used improperly. Manufacturers have taken steps in the past to avoid misuse, including adding warnings to product labeling, implementing risk management plans, and conducting interagency collaborations. But despite these efforts, the rates of misuse and abuse and accidental overdoses have risen over the past decade. Establishing a REMS for opioids will reduce risks while ensuring that patients who need them will have appropriate access."

Asked if the REMS will apply to drug applications that are pending, Dr. Jenkins said, "The letters went out to companies that have approved applications. These are either approved NDAs or approved ANDAs – generally products that are extended-release products. Some are transdermal patches. They are not, in general, the more immediate-release products, although some of the methadone products that are on (the list) are immediate-release products. It's not all opioids; it's certain opioids that we think require the REMS, and I can't comment on pending applications under review."

Asked if any of the products affected already have risk management programs in place, Dr. Jenkins said, "Several of these products already have risk management plans that were implemented before we had the REMS authority. The exact components of the REMS will be something we'll be working out in the course of hearing pubic input and working with the manufacturers. We'll also be working with the DEA to ensure that these products are used properly and safely. We believe that there needs to be significant improvement in the education about the safety of these products – for prescribers and patients. The actual exact details remain to be worked out…We don't believe that the risk management plans (already in place) have fully met the goals that we'd like to achieve, so we expect the REMS program will go beyond what is present in the (current) risk management plans."

Dr. Jenkins said that he envisions a class-wide REMS that would include all the opioids, "We do believe that the best way to effect this REMS will be for it to be the same program for all the affected products…(At the meeting on March 3, 2009, we will) emphasize the need to develop one system. The legislation…calls for one system for innovators and generics except in rare circumstances. This is

Products Affected

Generic name	Marketed name	Manufacturer
Brand drugs		
Fentanyl	Duragesic extended-release transdermal system	Johnson & Johnson/Ortho McNeil Janssen
Hydromorphone	Palladone extended-release capsules *	Purdue Pharma
Methadone	Dolophine tablets	Roxane Laboratories
Morphine	Avinza extended-release capsules	King Pharmaceuticals
Morphine	Kadian extended-release capsules	Actavis
Morphine	MS Contin extended-release tablets	Purdue Pharma
Morphine	Oramorph extended-release tablets	Xanodyne Pharmaceuticals
Oxycodone	OxyContin extended-release tablets	Purdue Pharma
Oxymorphone	Opana extended-release tablets	Endo Pharmaceuticals
Generic drugs		
Fentanyl	Fentanyl extended-release transdermal system	Actavis
Fentanyl	Fentanyl extended-release transdermal system	Lavipharm
Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
Fentanyl	Fentanyl extended-release transdermal system	Teva Pharmaceutical Industries
Fentanyl	Fentanyl extended-release transdermal system	Watson Pharmaceuticals
Methadone	Methadone tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Novartis/Sandoz
Morphine	Morphine sulfate extended-release tablets	Endo Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	KV Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	Mallinckrodt
Morphine	Morphine sulfate extended-release tablets	Watson Pharmaceuticals
Oxycodone	Oxycodone extended-release tablets	Mallinckrodt
Oxycodone	Oxycodone extended-release tablets **	Impax Labs
Oxycodone	Oxycodone extended-release tablets **	Teva Pharmaceutical Industries

* no longer marketed, but still approved ** Discontinued

going to be the largest risk management effort we've undertaken – 21 million prescriptions – so it needs to be coordinated among sponsors, the pharmacy system, and the healthcare system in general…Products that are not being requested to have REMS tend to be immediate-release products…It is easiest to say what is covered. A lot of products in the opiate class are not being covered. We believe focusing on the products listed will have the most impact on the inappropriate use and the unsafe use."

Asked what prompted the FDA to go ahead with the plan, Dr. Jenkins said, "We've been concerned about this issue with these products for quite some time…When we got the new authority under FDAAA, we revisited (the issue) to see if there was something more we could do with our new authority, and once we got the interpretation, we started working through what type of program would be useful and how we would go about implementing it…Our focus is going to be making sure that the prescribers are educated and understand the risk associated with the products and the appropriate patient populations that should receive these products. We continue to see reports of patients who do not have chronic pain who have acute self-limiting conditions who get these transdermal products and extended-release products. They're getting into trouble, and some of them are dying. We want to make sure that the patients are educated…(about) how to destroy them if they are not used at end of the prescription… and (on how to) try to avoid letting the products become available to family members or others in the community who may not understand how to use them safely."

Asked about the isotretinoin and thalidomide risk management programs, Dr. Jenkins said, "Those programs…were put in place before FDAAA. They were initially risk management plans, but we put a notice in the Federal Register last spring and deemed those to be REMS, and the companies were required to submit those programs and convert them to REMS. All those are being reviewed, and while that process is ongoing the existing programs remain in place." Since the FDA received the REMS authority in March 2008 he said our new REMS programs have been approved, "with elements to ensure safe use. One of the ones I recall was Entereg (Adolor/GlaxoSmithKline, alvimopan), a product used in the hospital after a patient has abdominal surgery…The largest restricted program is probably the isotretinoin program, which has been in place a few years and is retroactively being converted into a REMS. That submission is still under review."

Asked why the FDA is targeting extended-release drugs, Dr. Jenkins said, "We've seen the data that leads us to being concerned about extended-release and high potency (drugs). There's no doubt that others can be misused or abused as well, but we're focusing on these products because they generally contain very high doses of the product; or if they don't contain a high dose, the extended-release mechanism can be defeated …We're focusing on these because they seem to be causing the most problems with serious adverse events and death, and they need to be used very carefully…(Some) patients don't understand how to take them correctly and maybe chew the extended-release tablets, so they get an immediate release of high opioid dose…We continue to see case reports of someone with a sprained ankle given a fentanyl patch or extended-release oxycodone tablet."

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