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Mandatory FDA restrictions on the way for isotretinoin: voluntary programs deemed ineffective.

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The Food and Drug Administration will scrap isotretinoin's handful of voluntary risk management programs in favor of one mandatory, more restrictive system like that used for thalidomide.

Although many dermatologists are relieved that isotretinoin won't be removed from the market, some expressed concern that the FDA's decision may prompt more dermatologists to stop prescribing the teratogenic ache drug--and could push patients to seek the drug from sources on the Internet.

"In the long run, this [policy] is short sighted," said Hilary Baldwin, M.D., vice chair of dermatology at the State University of New York, Brooklyn. "'I'm just very sad."

The new program is expected to go into effect this year. Prescribing physicians, dispensing pharmacies, and patients will be required to register in a program known as RiskMAP (risk minimization action plan). This program will be run by the drug-development services company Convance Inc., which has contracted with Roche, the manufacturer of Accutane, as well as with the manufacturers of generic isotretinoin.

The Nov. 23 announcement came the week after a senior FDA official--during a Senate hearing on the abrupt recall of the COX-2 inhibitor Vioxx because of reports linking it to cardiovascular events--named isotretinoin as one of five drugs that ought to be either withdrawn from the market or more severely restricted.

The close timing of the FDA's announcement and the well-publicized Senate testimony may have been coincidence, however. In a statement, the FDA said it was able to make the announcement now because an agreement was reached with Celgene Corp., which owns a patent on the STEPS (System for Thalidomide Education and Prescribing Safety) program, on which the isotretinoin program will be based.

A more restrictive risk management program had been expected since March 2004, when two FDA advisory committees concluded that Roche's SMART (System to Manage Accutane Related Teratogenicity) program and similar programs for generic isotretinoin had failed to pre vent pregnancy exposures (SKIN & ALLERGY NEWS, April 2004, p. 1).

At the meeting of those committees, data were presented that showed 127 pregnancy exposures

occurred in the year before the SMART program was implemented, compared with 120 pregnancy exposures in the year after, despite the fact that isotretinoin prescriptions declined by 23%.

Moreover, when the SMART program and the others were approved by FDA, the agency had threatened that further restrictions would be imposed unless 60% of women who were written a prescription enrolled in a voluntary, ongoing survey run by the manufacturers. That goal was not met.

The Shape of Restrictions to Come

Under RiskMAP, the following conditions must be met before isotretinoin can be dispensed: documentation of patient education by the provider; a signed informed-consent form; and a negative pregnancy test, which will have to be repeated in order for the patient to obtain refills. More specific details of the program have yet to be determined.

A major advantage of the new program is that physicians will no longer have to ad here to the requirements of four similar but distinct programs, each run by different manufacturers. Some physicians found that confusing, the FDA said. Instead, there will be a single, unified program covering all brands of isotretinoin.

In contrast to what has occurred under the isotretinoin risk management programs, pregnancy exposures to thalidomide have been well controlled under the STEPS program. About 4,000 women of childbearing age have taken thalidomide since it was reintroduced into the market for the treatment of cancer and leprosy. Only one pregnancy exposure has occurred, resulting in a spontaneous abortion.

The official response to the FDA action from the American Academy of Dermatology was one of relief that there is no plan to withdraw isotretinoin from the market.

"Let me assure you that isotretinoin has not been taken off the market as a result of this [Senate] hearing: it will continue to be available for your patients," stated AAD President Boni E. Elewski, M.D., in a letter mailed to academy members.

The letter notes that the academy is being given an active role in designing the new program, and it urges dermatologists to remain conscientious about fulfilling the present prescribing program requirements because it is a time of increased 'scrutiny."

Dermatologists write 80% of the prescriptions for isotretinoin.

Unofficially, however, some dermatologists contacted by this newspaper were chagrined. "It's unfortunate," said Alan R. Shalita, M.D., professor and chair of dermatology at the State University of New York, Brooklyn, and an acne researcher. "We'll just have to live with whatever restrictions they impose."

Dr. Shalita's colleague, Dr. Baldwin, said she too thought the new program would mean that

fewer physicians would be willing to prescribe isotretinoin. That will probably drive patients to the Internet to get their medication, she added, leaving more patients without any medical supervision at all.

There are more than 30 brands of isotretinoin made and sold worldwide, she noted.

"I'm also worried that they are going to get 'Pete's" isotretinoin, and it is not even going to have isotretinoin in it," she said.

Thalidomide may not have had as many pregnancy exposures as isotretinoin, but that does not necessarily mean the thalidomide program will work the same way for isotretinoin, Dr. Baldwin said.

Most patients treated with thalidomide are older, and they are being treated for multiple myeloma. Therefore, they are very sick and probably not inclined to have sexual intercourse.

The FDA's action also prompted a statement from Rep. Bart Stupak (D-Mich.), a well-known critic of isotretinoin, whose son committed suicide while taking the drug.

Stupak's statement suggested that the wrangling over isotretinoin may continue. The congressman vowed to respond if the FDA's final risk management program was not strict enough, and he called for hearings specifically on isotretinoin.

DATA WATCH Isotretinoin Prescribing Declines 1999 1.9 2000 2.0 2001 1.6 2002 1.3 2003 1.2 Note: table made from line graph. Note: Based on data for more than 2 billion phar macy, hospital, and medical transactions per year in the United States, Source: Verispan