FDA Alert for Healthcare Professionals

Isotretinoin (marketed as Accutane)

FDA ALERT [11/2005]: Start Dates Have Been Changed for the iPLEDGE Program. FDA approved a strengthened risk management plan for Accutane and generic isotretinoin on August 12, 2005, to make sure females do not become pregnant while taking this medicine. Isotretinoin causes birth defects. This new plan is called iPLEDGE. For details of iPLEDGE go to http://www.fda.gov/cder/drug/infopage/accutane/default.htm. The iPLEDGE program was originally scheduled to begin on November 1, 2005. To allow more time for registration and activation, the implementation dates of the iPLEDGE program have been revised. The date by which wholesalers and pharmacies must be registered/activated in IPLEDGE has been changed from November 1, 2005 to December 30, 2005. The starting date to begin patient registration and qualification in iPLEDGE has been changed from November 1, 2005 to December 30, 2005. By March 1, 2006, only prescribers registered and activated in iPLEDGE will be able to prescribe isotretinoin and only patients registered and qualified in iPLEDGE will be able to be dispensed isotretinoin.

[07/2005] SUICIDAL THOUGHTS OR ACTIONS: In addition to the strengthened risk management program, FDA continues to assess reports of suicide or suicide attempts associated with the use of isotretinoin. All patients treated with isotretinoin should be observed closely for symptoms of depression or suicidal thoughts, such as sad mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating, or for mood disturbance, psychosis, or aggression. Patients should stop isotretinoin and they or their caregiver should contact their healthcare professional right away if the patient has any of the previously mentioned symptoms. Discontinuation of treatment may be insufficient and further evaluation may be necessary. [Action taken 08/12/05 Labeling revision]

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of isotretinoin, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

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Recommendations

- All patients treated with isotretinoin should know the risk of birth defects if exposed during pregnancy. Females of child bearing potential must use 2 separate, effective forms of contraception at least one month before, during, and for 1 month after stopping isotretinoin to make sure the drug is gone from the body. Physicians must input information into the iPLEDGE system monthly, including pregnancy test information for females of child bearing potential. Females of child bearing potential must also interact with the iPLEDGE system monthly. Patients cannot donate blood while on isotretinoin nor for one month after stopping treatment.

- Physicians are reminded that isotretinoin is marketed with a risk minimization action plan (RiskMAP) to reduce fetal exposure to the drug. By March 1, 2006, only iPLEDGE pharmacies will be able to dispense isotretinoin based on prescriptions from only iPLEDGE physicians for iPLEDGE patients.

- All patients treated with isotretinoin should be observed closely for symptoms of depression or suicidal thoughts and referred to a specialist if necessary. Discontinuation of the drug may not be sufficient; psychiatric evaluation and further intervention may be necessary to prevent patients from harming themselves.

- All patients should be informed to discontinue isotretinoin, and inform his/her healthcare professional right away if any of the following happens:
    - Start to feel sad or have crying spells
    - Lose interest in activities once enjoyed
    - Sleep too much or have trouble sleeping
    - Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
    - Have a change in appetite or body weight
    - Have trouble concentrating
    - Withdraw from family or friends
    - Experience loss of energy
    - Experience feelings of worthlessness or inappropriate guilt

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- Start having thoughts of self-harm, or suicide
- Start acting on dangerous impulses
- Start seeing or hearing things that are not real

Data Summary

Some of the serious adverse event reports FDA has received regarding isotretinoin include birth defects and psychiatric effects (e.g., suicide ideation and suicide). Isotretinoin is a well established teratogen. Although causality has not been established for isotretinoin and psychiatric events, the following information is important to consider:

- Preclinical and neuroimaging data suggest that isotretinoin produces behavioral effects (i.e. activation) in rats, impairment of neuronal division in the murine hippocampus, and reductions in orbitofrontal brain metabolic rates in humans. This preclinical and neuroimaging data may suggest biological plausibility for the suspected psychiatric adverse events associated with isotretinoin.

- From isotretinoin's initial marketing in 1982 through August 2004, 4,992 spontaneous reports of psychiatric disturbances associated with using isotretinoin in patients in the United States have been submitted to the FDA.

- The number of reported suicides among isotretinoin users in the United States was 190 through January 2005. Between 1982 and 2002, there were 165 reported suicides, which were fewer than the 220 predicted based on U.S. vital statistics data. However, because the degree of under-reporting of suicides is unknown, the fact that the reported number is lower than the predicted number cannot be interpreted as evidence against a causal association.