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FDA Drug Safety and Risk Management
and Dermatologic and Ophthalmic Drugs
Advisory Committee Meeting on

Isotretinoin (Accutane)

February 26, 2004

Public Citizen Health Research Group: 20+ Years of Isotretinoin Actions

- September 8, 1983 – Petition submitted urging patient package inserts and black box warning about birth defects and life-threatening adverse events
- July 17, 1984 – Letter to FDA advocating improved pregnancy surveillance and lower dosing regimens
- April 26, 1988 – Testimony before FDA Dermatologic Drug Advisory Committee describing Accutane as an imminent public health hazard and proposing removal from the market if these tight restrictions are not effective:
 - Limit prescribing to dermatologists who file sworn affidavits stating they will adhere to the stated indications for the drug
 - Mandate written informed patient consent
 - Include pregnancy testing requirements in the black box warning and mandate pregnancy and adverse event reporting to the FDA
- May 17, 1988 – Petition to FDA outlining above recommendations

Public Citizen Health Research Group: Over 20 Years of Isotretinoin Actions

- May 8, 1989 – Testimony before FDA Dermatologic Drug Advisory Committee urging removal of Accutane from the market unless restrictions previously proposed are immediately adopted
- June 1, 1989 – Testimony before FDA Fertility and Maternal Health Drugs Advisory Committee reiterating previous recommendations
- May 21, 1990 – Testimony before FDA Joint Fertility and Maternal Health and Dermatologic Drug Advisory Committee again proposing restricted use
- September 18, 2000 – Testimony before FDA Dermatologic and Ophthalmic Drugs Advisory Committee recommending a patient Medication Guide and again advising removal from the market in one year unless previously proposed restrictions are instituted and are effective

CDC Testimony Before this Committee: May, 1989

- “The birth of babies with defects caused by fetal exposure to Accutane is unnecessary.”
- “...FDA decision to allow the marketing of Accutane [is] a failed regulatory experiment.”
- “A decision to depend on better contraception alone, without active intervention to reduce the number of users, is a decision to leave the number of affected babies at an unacceptably high level.”
- “Perhaps a formal IND...would be a suitable mechanism...to reduce the frequency of Accutane embryopathy.”

Reported Accutane Pregnancy Exposures: 1982-2000*

- Exposed pregnancies 1995
- Elective Abortions 1214
- Live Births 383
- Infants with birth defects 162

*Data presented by FDA at Derm & Ophth.
Drugs Advisory Meeting 9/18/00

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Estimation of Total Actual Pregnancy Exposures During First Year of S.M.A.R.T

- 156,800 “unique” women given the drug*
- Estimated pregnancy rate of 0.35%*
- Total number of pregnancies = 548 (this number is 4.6 times higher than the 120 pregnancies spontaneously reported*)

Estimation of the Number of Elective Abortions During First Year of S.M.A.R.T.

- Of 61 pregnancies with known outcomes, 48/61 or 78.7% resulted in elective abortions*
- Applied to the 548 estimated pregnancies, there would have been 431 elective abortions in that year

Estimation of the Number of Deliveries During First Year of S.M.A.R.T.

- Of 61 pregnancies with known outcomes, 7/61 or 11.5% resulted in deliveries*
- Applied to the 548 estimated pregnancies, there would have been 63 deliveries
- Based on estimates, this would result in 16 infants with birth defects and 31 with mental retardation (estimated 25% birth defects and 50% mental retardation)

Failure of S.M.A.R.T. and New Roche Proposals to Seriously Address Two Major Issues

- 95+% reduction in prescribing: CDC estimated in 1989 that there were no more than 4000 women of child-bearing age with severe cystic acne. Adjusted for population growth, this number may now be 6000. Given that there were 156,800 “unique” women of child-bearing age who got the drug in 2002-2003*, this represents a twenty-six fold excess in prescribing over the number of on-label prescriptions.
- Mandatory pregnancy test results (not just assurance) before and monthly as prerequisite to getting prescription

*CDC estimated 70,000 women getting the drug in 1989

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Rationale for Withdrawal of Isotretinoin from the Market

- Twenty years of failed voluntary and, more recently, mandatory restrictions have led to a total of more pregnancy exposures because the total number of prescriptions has increased.
- As we recommended in 1988 and the CDC suggested the next year, we now propose a ban on marketing with subsequent availability only under a tightly controlled IND as the only feasible way to significantly reduce prescriptions and pregnancy exposures.

Restrictions of IND

- Photographic proof of severe cystic acne confirmed by an independent group of dermatologists
- A written record for each patient of adequate previous treatment and recalcitrance to it
- Written statement of contraceptive practices and provision of a copy of this and negative pregnancy test in order for the drug to be dispensed each time

Summary

- The S.M.A.R.T program is clearly a failure. Without these proposed IND restrictions, this administration and this advisory committee will continue to put its imprimatur on the reckless use of a drug that each year causes the need for hundreds of abortions and results in many seriously deformed infants with birth defects and/or mental retardation. This is one of the two worst epidemics of preventable serious birth defects ever seen in the U.S. It is time to end the more than twenty years of voluntary restrictions that have failed to reduce its prescribing for more than twenty times as many women as would be using the drug if it were limited to the approved indications.