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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **October 20, 1988**

TO: Director, Division of Anti-Infective Drug Products (HFD-520)

FROM: Section Chief, Epidemiology Branch

THROUGH: Acting Chief, Epidemiology Branch (HFD-733) BVS 10-24-88

THROUGH: Deputy Director, Office of Epidemiology and Biostatistics (HFD-701) CA 10/25/88

SUBJECT: "Dear Doctor" letter and label for Accutane

Three weeks ago, I received a copy of the Accutane "Dear Doctor" letter in the mail, outlining the new recommendations for product usage as well as the new product labeling. This material states that there is "an extremely high risk that a deformed infant will result if pregnancy occurs while taking Accutane... Potentially all exposed fetuses may be affected." Further on, the physician and patient are instructed to "discuss the desirability of continuing the pregnancy," should pregnancy exposure occur. The effect communicated by this wording to the patient and her physician is that there is virtually a 100% risk of severe birth defect and that induced abortion should be performed.

The description of fetal risk presented here does not appear balanced and is not supported by the data available to the Agency. In his 1985 article on Accutane, Dr. Edward Lammer published data suggesting a birth defect rate of about 14% among women with a first trimester exposure to the drug.[1] This figure was derived from spontaneous reports of pregnancy exposure and may have suffered from reporting bias which would produce a falsely high estimate for the rate of birth defect. More recently, Lammer has published an abstract which suggests that the risk of abnormality may be up to 23% among first trimester exposed pregnancies surviving beyond 20 weeks gestation.[2] This figure is based upon the pregnancy exposures published in 1985 as well as some others subsequently referred to Lammer's attention. Because these represent referral exposures, it is possible that this group of pregnancies is biased toward "higher risk" exposures in which the referring physician believed that a

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[1] Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. N Engl J Med 1985; 313:837-41.

[2] Lammer EJ, Hayes AM, Schunior A, Holmes LB. Risk for major malformation among human fetuses exposed to isotretinoin (13-cis-retinoic acid). Teratology 1987; 35:68A.

birth defect was likely to occur. A better way to estimate the risk of birth defect would be to observe the experience in a population of exposed women, where there is freedom from potential referral bias. Although numbers are small, some such data is available from Michigan Medicaid.

In the cohort of 928 women with suspected first trimester exposure to Accutane in Michigan Medicaid, there were 13 pregnancies reaching delivery. Computerized linkage of the mothers and the infants Medicaid profile could be achieved in 12 cases. Seven of the deliveries were reported as normal. Among the remaining five, there was one stillbirth, and one perinatal death in a premature infant. The medical records we have obtained on this death do not indicate that Accutane had any role in the premature birth, and they make no mention of any birth defect being present. Medical records for the stillbirth are not yet available for our review.

Of two deliveries carrying an ICD-9 diagnosis code for "craniofacial abnormality," we have obtained the primary medical records for one. In this child, the ICD-9 code referred to a caput hematoma resulting from the delivery itself. This is a routine and insignificant complication seen in some deliveries and is totally unrelated to Accutane exposure. The child is otherwise normal. We have not yet been able to obtain the primary records for the other delivery carrying this ICD-9 code. However, from the computerized profile of medical diagnoses and prescriptions for this latter child, we know that there is no further reference to any craniofacial abnormality, suggesting that this also is not a true birth defect. There is one other delivery for which more information is needed. In this case, there is apparently no Medicaid record for the child raising the possibility of adoption, emigration out of Medicaid, or perinatal death. We are still attempting to clarify the outcome in this case.

From this description of 12 deliveries with suspected first trimester exposure to Accutane, there have been no abnormalities which we can attribute to an Accutane exposure. The one perinatal death of which we are certain seems to be probably related to prematurity and low birth weight. The two cases with ICD-9 codes for "craniofacial abnormality" probably represent minor birth trauma and are not related to Accutane exposure. Medical records are still needed for one of these. The remaining case of stillbirth requires further investigation as does the case in which no Medicaid profile exists for the delivery. These data suggest that the risk of birth defect among pregnancies with first trimester exposure to Accutane may be much lower than previously reported. Admittedly, this data is crude and followup needs to be done on all 12 women with deliveries in order to validate both the pregnancy outcome and the first trimester exposure to the drug. But it also points to the value of population-based prospective data to measure the birth defect risk rather than relying on referred cases from multiple sources which may provide a biased overestimate of risk.

The purpose of this is not to dispute that Accutane is a teratogen. Data from the literature and the FDA spontaneous reports system show that Accutane can cause birth defects. However, the magnitude of risk is not known with certainty, and the data available suggest far lower risks of birth defect than are implied in the "Dear Doctor" letter and the product labeling. The

literature estimates of birth defect risk following first trimester exposure may be artifactually high because of factors of reporting and referral bias.

Another aspect of the problem which the current mailing ignores is that not all birth defects caused by Accutane are of comparable severity and many can be treated. Also, many of the abnormalities are limited solely to disorders of the outer ear or external ear canal. Lammer's abstract fails to distinguish these defects.[2] At the April 1988 Advisory Committee meeting, Dr. Lammer showed some slides of children with subtle and mild abnormalities of the cheeks which did not become evident until several years of age. The children were otherwise totally normal. It is not clear if Lammer has included "defects" such as this in his 23% estimate for Accutane induced birth defects. Finally, data presented to the Agency in 1984 suggests that if Accutane is stopped by the date of the first missed menstrual period, that there may be no additional risk of birth defect compared to non-exposed pregnancies. Information such as this may be very important to women to be aware of when they experience a pregnancy exposure to Accutane.

I surveyed members of the epidemiology branch to answer the question: after reading the "Dear Doctor" letter and labeling, what do you estimate the risk of severe birth defect to be in the offspring of a woman exposed to Accutane while pregnant? Of nine surveyed (eight physicians, one dentist), eitht believed the risk to be near 100% on the basis of the information presented. The one other branch member believed the risk was high but declined to quantitate what "high" meant. Several of those surveyed volunteered that the wording of the "Dear Doctor" letter was likely to pressure women into having an induced abortion. Others noted that the overall wording left the impression that exposure during the second or third trimester was also dangerous. One other believed that rather than warning a woman to not become pregnant while on Accutane, that the symbol of the pregnant woman with a line through her suggested that an abortion be performed if pregnancy exposure occurred.

These factors are important because of the use to which such information as is contained in the product label and "Dear Doctor" letter will be put. Physicians and patients will rely on this information for decision making and the current mailing seriously pushes them toward abortion. The addition of a pen drawing composite of the most severe physical abnormalities which may occur after Accutane pregnancy exposure is also a potential problem. In the context of the rest of the label, I believe such a drawing promotes the misleading impression that the worst case always happens by tapping into visual and emotional sensibilities. Rather than "educating" physicians and patients, this drawing may further serve to heighten emotion, cloud judgement, and pressure decision making toward abortion once an exposure has occurred.

Although the Agency's intention in approving the wording of the labeling and "Dear Doctor" letter may have been to frighten women and physicians away from using Accutane, a much different interpretation by the readers of this material seems likely. The information sent out by the manufacturer leads the reader to the conclusion that pregnancy exposure to Accutane will inevitably lead to severe birth defects and that induced abortion be performed. As outlined above, the risk of birth defect is not known with certainty. The highest estimate (23%) may include late appearing and/or minor abnormalities and also

be subject to reporting and referral bias which would tend to make this an inflated estimate. Also, this data has not been subjected to careful Agency or peer review and may be subject to error. In the general population (where problems of referral/reporting bias are not operating), the risk may be much lower.

Related to this, the labeling does not convey important ancillary information that not all the defects are of comparable severity and that a spectrum exists which may be important for a woman to be aware of in the event of pregnancy exposure.

I bring this to your attention because I believe that the material sent to me and thousands of other physicians, as well as the educational campaign associated with it, pushes both women and physicians toward the selection of induced abortion once a pregnancy exposure has occurred. This results from the dual effect of inaccurate and misleading presentation of available information concerning birth defect risks and wording referring to "the desirability of continuing the pregnancy," both of which implicitly recommend that abortion be performed. I do not believe that these materials should be used for such purposes.

David J. Graham

David J. Graham, MD, MPH

cc:
Bilstad (HFD-500)
Evans/Huene/Bostwick (HFD-520)
Faich/Anello (HFD-700)
Stadel/Graham (HFD-733)
DRU 1.7 Isotretinoin