9

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: April 6, 1989

FROM: Medical Epidemiologist, Accutane Monitoring Group

SUBJECT: Accutane status update

TO: Chairman, Accutane Monitoring Group

Summary

Following the April 1988 advisory committee meeting on Accutane, the Agency adopted a number of interventions the purposes of which were 1) elimination of pregnancy exposure and 2) reduction of product usage to that specified in the labeling. The sponsor was instructed by regulatory letter to among other things perform postmarketing studies to assess the effect of the interventions adopted.

1) Pregnancy exposure to Accutane continues to the present. Incidence is not certain, but based on spontaneous reports alone, is at least 1 per 2000 women. Given that underreporting of adverse reactions in general is extensive and that the majority of exposure cases end with spontaneous abortion (40% of clinically recognized first trimester pregnancy exposures) and induced abortion (60% of remaining first trimester pregnancy exposures), neither of which are customarily reported as adverse reactions by physicians or the sponsor, actual incidence is likely to be substantially higher. From data on contraceptive failure rates, it is conservatively estimated that at least 600 women experienced pregnancy exposure to Accutane in 1988.

2) Accutane usage has not changed in a meaningful or substantive way. In 1988, at least 70,000 women of childbearing age were started on Accutane, exceeding by more than 15-fold (1500 times) the estimated annual incidence in this group of severe recalcitrant cystic acne unresponsive to other therapies (the labeled indication). The observation of possible reduction in refill prescriptions in Q488 will not materially reduce the risk of pregnancy exposure, which is almost exclusively encountered during the first and to a lesser extent, the second and third months of treatment. In addition, Accutane is widely overused in men.

3) The sponsor has not submitted a scientifically acceptable study proposal. Rather, they have proceeded with a survey proposal rejected twice by the Division of Epidemiology and Surveillance as well as by two internationally recognized authorities in the field. The study was rejected on the grounds that it was incapable of answering questions of greatest concern to the Agency. We estimate enrollment in this study to be less than 3% of women eligible to participate.

FDA interventions have not achieved their objectives and there is no reasonable expectation of their being achieved in the forseeable future.

Background and history

The purpose of this communication is to summarize the most recently available data relating to Accutane usage and pregnancy exposure and to describe the current status of postmarketing surveillance efforts for Accutane.

The sponsor (Roche) was instructed in May, 1988 to design and carry out postmarketing studies acceptable to the Agency. The purpose of these studies was to assess the effect of FDA interventions designed to eliminate pregnancy exposure to this drug and to bring product usage into conformance with its labeled indication. The Division of Epidemiology and Surveillance (DES)

received a draft protocol proposal for such a study from the Slone Epidemiology Unit (SEU) in June. This proposal had a number of serious scientific deficiencies which rendered it unacceptable. This evaluation was transmitted to Dr. Alan Mitchell, the principle investigator for this study at SEU.

In August, 1988, DES received the formal submission of a postmarketing study proposal. This proposal was identical to the draft submitted two months earlier. The submitted proposal was reviewed for its epidemiologic merit and its ability to answer fundamental questions of importance to FDA. As before, the proposed study was found to be flawed and potentially substantially biased at its foundation. It was the opinion of the medical officer reviewing this proposal that registered release was necessary to ensure an unbiased measurement of Accutane pregnancy exposure. The Epidemiology Branch Chief concurred with the evaluation stating that total ascertainment of pregnancy exposure was essential, and he listed criteria to be met by any study of this question. This evaluation was transmitted as a memorandum to the Division of Anti-Infective Drug Products in October, 1988. A copy was sent to Roche by the Division. In addition to the DES assessment, evaluative opinion was obtained from Dr. James Schlesselman, professor of Epidemiology and Biostatistics at the Uniformed Services University of the Health Sciences, and Dr. Barbara Hulka, professor and chairman, department of Epidemiology, University of North Carolina School of Public Health. Both of these individuals are internationally recognized experts in the field of epidemiology and both found the SEU/Roche study proposal to be so potentially biased that it was unlikely to produce reliable or accurate results. Dr. Schlesselman added that the best study design was one based on total registration of Accutane recipients.

A meeting was held later in October with representatives from Roche and SEU to discuss the issues of bias in the study and ways to reduce or eliminate it. The sponsor was told the reasons why their study proposal was not scientifically acceptable and they agreed to submit another proposal. At the end of this meeting, Dr. Mitchell stated privately that he agreed with the evaluation of the SEU proposal which we had written and that registered release was the best way to answer questions relating to Accutane pregnancy exposure. Also at this time, the Accutane Monitoring Group (AMG) was formed within the Agency to ensure inter-office coordination and oversight of Roche efforts pertaining to Accutane surveillance and study.

In late November, 1988 a telephone conference call was held between members of the AMG (Nelson, Huene, Graham) and representatives of Roche and SEU. During that call, the position of the AMG (and Agency) was again clearly stated by Drs. R. Nelson and D. Graham. Roche and SEU were told that FDA did not accept the study which had been proposed because it would most likely give misleading results which would be favorable to the sponsor but which were derived from biased data not representative of all women using Accutane. During this conversation, Dr. Sidney Shapiro, professor of Epidemiology at Boston University and Director of SEU expressed the opinion that registered release would produce the best study.

Later in the discussion, Dr. Mitchell asked what the FDA response would be if Roche went ahead with the SEU proposal. As you recall, we turned the volume switch off on the speaker phone to discuss this privately before responding, not realizing that the Roche/SEU participants were still able to hear our entire conversation. The three of us present were in complete agreement that it would be better not to do such a biased study but that we did not have the legal authority to prevent its being done. Among our fears was that Roche would attempt to use the results from this study to force the Agency to back away from Accutane, and that they would use it to make claims that pregnancy exposure had been eliminated when we knew that the study had virtually no possibility of demonstrating pregnancy exposure because of biased design. Our response to Dr. Mitchell's question was that FDA had rejected the study submitted by Roche and that the results from such a study would not be used by the AMG in formulating

recommendations because the study was incapable of accurately and reliably answering the questions of greatest importance. We strongly encouraged them not to proceed with this survey, but acknowledged that we did not have the ability to prevent them from doing it. We were then informed that Roche intended to carry out the SEU survey. After the call, we discussed the possibility that Roche would use this ongoing SEU survey as an excuse to delay designing and carrying out an epidemiologic study acceptable to FDA.

The AMG next met with Roche/SEU in February, 1989. Among items discussed were the format of future quarterly reports from Roche on Accutane usage and reports of pregnancy exposure. The issue of a postmarketing study to assess the effect of FDA interventions was also discussed again. FDA objections to the SEU survey and the FDA criteria for what was needed for a study to be acceptable were once again stated. The sponsor promised that a final proposal would be submitted shortly. As of this time, nine months after the initial rejection, a final proposal has not been received or accepted.

Presentation of Data

Information on Accutane usage was obtained from the National Prescription Audit (NPA) which obtains prescription data from a panel of retail pharmacies across the contiguous US and provides estimates of national product usage, and from the National Disease and Therapeutic Index (NDTI) which obtains data from a panel of 2000 physicians across the US on the drugs mentioned during patient encounters. NDTI can provide some insight into the demographics of the patient population as well as the health care provider involved. Caution must be used in interpreting NDTI trends because the physician panel from which these national estimates are derived is relatively small, resulting in wide confidence limits around the point estimate. For this reason, such data is best used for its "gestalt" value of what appears to be occurring overall.

NPA

The pattern of Accutane prescribing in the US is shown in Figure 1. Between 1983 and 1988, there was little change in annual numbers of prescriptions. The total number in 1988 was comparable to that of 1986 and only slightly lower than in 1987. Most of this slight decline was in the area of refill prescriptions as opposed to new therapy starts. Figures 2 and 3 show the average monthly number of new and refill prescriptions for Accutane by quarter for the last full three years of marketing. These data show that Accutane prescriptions in Q488 (fourth marketing quarter of 1988) were lower than the Q4 averages for 1986 or 1987. There was about a 20% decline in new and 25% decline in refill prescriptions in Q488 compared to Q487. However, this was still at the level of or greater than Q388. Figure 4 displays this NPA data by month and shows several things. First, there is an apparent seasonality to Accutane prescriptions with falls in use during the months from May or June to September or so. Also, the seasonal nadir in prescriptions in 1988 was no lower than that in 1986 or 1987. Finally, Accutane prescriptions were increasing in Q488 although at a slower rate than in 1987.

The distribution of prescriptions by dosage is shown in figures 5, 6 and 7. Over the years 1986 to 1988, there has been a small decline in 40mg size and a small increase in 20 mg size prescriptions (figure 5). This small decline in 40 mg prescriptions was proportionately greater in the area of refill prescriptions (figure 6) than it was for new prescriptions in 1988 compared to 1987 (figure 7).

NDTI

Total mentions for Accutane for the years 1983 to 1988 are shown in figure 8. The shape of this distribution bears close resemblance to that for NPA prescription data (figure 1). Use of Accutane in women 15-44 by year is shown in figure 9. Total use in 1988 is comparable to that of years 1984 through 1986, but is down somewhat from 1987. The majority of this decrease in usage was in the category of continued (refill) use. New use of Accutane in women of childbearing age was greater in 1988 than in 1985 or 1986, but down somewhat from 1987 levels. A similar though not identical situation was seen with Accutane use in women not of childbearing age (< 15, > 44) and in men (figure 10). Accutane use in women 15-44 by quarter of marketing for the last three years is shown in figure 11. Although there have been fluctuations quarter to quarter, the overall level of new mention of Accutane therapy in women has remained more or less stable at about 20 thousand per quarter. Over the same period, there appears to have been a reduction in continued use. Except for the data point for Q387, new use of Accutane in women 15-44 has not changed substantively in 1988 compared to 1986 or 1987 (figure 12). By contrast, Accutane use in men shows little overall change in either new or continued categories (figure 13).

As a percentage of total Accutane use, usage in women 15-44 has remained

Discussion

Accutane usage

From the NPA and NDTI data available, several observations can be made. Overall Accutane usage measured by prescriptions has not changed very much in recent years. The majority of the small decline in prescriptions in 1988 has been related to refills. From monthly trend data, it appears that the reason for the slightly reduced number of prescriptions in 1988 is that there has been a slower rate of increase in prescriptions after the summer seasonal drop, which is most apparent in Q488.

There is marked seasonality to Accutane prescriptions, with reductions during the summer and early autumn months. Two processes may be operative. During the summer months, acne patients (who are otherwise generally healthy) may not visit their physicians as frequently because of vacations and other activities. Also, increased sun exposure may improve the acne of a number of patients, resulting in reduced visits to physicians because of acne. While sun exposure would not improve severe cystic acne, it could affect milder degrees of acne which comprise the majority of Accutane patients.

Although NDTI data is based on a relatively small sampling frame, it suggests that use of Accutane in women of childbearing age has not been substantively or meaningfully altered. Total use in women did decline modestly in 1988 compared to 1987 according to this data source. However, most of this decline was in the area of continued (refill) use. In terms of actual numbers, over 70,000 women age 15-44 were started on Accutane during 1988, which was not much change from previous years. This interpretation is supported by the fact that the percentage of total Accutane usage accounted for by women 15-44 has remained virtually unchanged since 1983. The combination of these threads of information strongly suggests that Accutane usage has not changed much during 1988 and that what changes might have occurred were not focused on women, but affected men as well and were primarily restricted to refill use.

The actual number of women 15-44 started on Accutane in 1988 may be higher than the NDTI estimate of 70,000. There were over 900,000 prescriptions for Accutane in 1988 NPA, figure 1) and usage by women constituted 44% of this for a total of 400,000 Accutane prescriptions in this group. If the average duration of therapy was the labeled five months, about 80,000 women were treated. If the average duration of therapy was shorter than this (supported by data on refills), say perhaps four months, 100,000 women may have been exposed to Accutane last year.

These findings must be interpreted against the background of what is known about the epidemiology of severe recalcitrant cystic acne (the labeled indication). As described in previous memoranda, cystic acne is a very uncommon disease. From NHANES, the data are: males are affected about 5.5 times more often than females; the disorder is extremely rare in males over age 44 and is virtually never seen in females over this age; the population prevalence in the US for all degrees of cystic acne severity is 1.9 per 1000 overall (3.3 per 1000 in males, 0.6 per 1000 in females). From references in the dermatologic literature (cited in previous memoranda), cystic acne occurs as a spectrum of severity from one or a few cysts to multiples of 10 or 100. During IND trials with Accutane, "severe" was operationally defined as 10 or more deep inflammatory cystic lesions of 0.4 mm diameter or greater. These trials had much smaller numbers of patients than are generally seen in major clinical trials because the number satisfying the definition of "severe" was very small. Duration of cystic acne is measured in years, with the median being on the order of 8-9 years. With this information from population based examination surveys and the dermatologic literature, estimates were previously derived for the number of women of childbearing age fulfilling the labeled indication for Accutane. The estimated annual number of incident cases of cystic acne meeting the labeled indication

for the drug in women of childbearing age is about 4,300. The number of men is about 20,000.

The number of women who were started on Accutane in 1988 was at least 70,000, more than 15-fold greater than expected. This is not much different than in previous years. In this same year, about 100,000 men were started on Accutane which is nearly a 5-fold excess over predicted. The proportion of Accutane use in women remained unchanged at about 44%, suggesting that there was not a focused reduction in product exposure among women.

The suggestion of a reduction in continued (refill) use among women but without a reduction in new therapy starts is most probably an indication that the duration of therapy with Accutane is shortening below the recommended five month course. This reduction in length of therapy is unlikely to have much of an effect on the risk of pregnancy exposure because the period of highest risk is during the first month or two of treatment. Data from Michigan Medicaid showed that among 13 suspected first trimester exposures to Accutane which reached delivery, eight (60%) received only one, four (32%) received two, and 1 (8%) received three prescriptions for Accutane. None received more than three prescriptions. From a published review of 37 cases of children with birth defects following first trimester Accutane pregnancy exposure, only three (8%) exposures definitely occurred on the fourth or greater number prescription. Thirty-one (84%) definitely occurred during the first or second prescription, with over 80% of these during the first.

Pregnancy exposure

FDA continues to receive reports of children with Accutane-related birth defects. The number is now 85, up from 66 a year ago. Insufficient time has passed for reports to be received of children exposed in-utero subsequent to the April 1988 advisory meeting.

From the manufacturer, FDA was informed of 9 new first trimester pregnancy exposures from Q488. The majority of these underwent induced abortion. During this quarter, about 20,000 women began new therapy with Accutane. This leads to a spontaneously reported pregnancy exposure rate of about 1 per two thousand women treated.

Given what is known about underreporting of serious adverse reactions, it is likely that FDA has learned of only a fraction of actual first trimester pregnancy exposure events. The degree of underreporting is likely to be even greater than that reported for other drugs in the literature where reporting efficiency ranges between 10% and 30%. The reason for this is because the majority of Accutane pregnancy exposures end with either spontaneous or induced abortion and physicians do not customarily report such outcomes as adverse drug reactions. Dr. Lammer has reported that first trimester exposure to Accutane may result in spontaneous abortion in 40% of clinically recognized pregnancies (a two-fold increase over the background rate for this event). It was previously shown that induced abortion occurs in 60% of remaining exposed pregnancies (this also is a two-fold increase over background). The end result is that fewer than 25% of first trimester exposed pregnancies reach delivery. Underreporting of pregnancy exposure is consequently quite high, probably exceeding that for other serious adverse reactions. The conclusion to be drawn from these findings is that pregnancy exposure to Accutane continues and that the actual incidence is high.

Another line of reasoning leads to a similar conclusion. From NDTI data, new therapy starts with Accutane in women of childbearing age are not changing very much from previous levels. In 1988, from 70,000 to 100,000 women 15-44 were started on Accutane (about 1 per 800 women in the US). Assuming an average therapy duration of 4 months (a decrease from the labeled recommendation of 5), this would translate to about 23,000 to 33,000 women-years of pregnancy risk on

Accutane. Published data show an irreducible failure rate of oral contraceptives of 2.5 per 100 women-years. Assuming that all women started on Accutane in 1988 practiced oral contraception (a big assumption because available data suggest that one-third practice no contraception and others use non-OC methods), we would expect at least 600 to 800 recognized pregnancy exposures to Accutane to have occurred. The actual number is likely higher.

Postmarketing study efforts

The sponsor has not submitted a study proposal to assess the effect of FDA interventions that is scientifically acceptable. It has proceeded with a survey protocol which was rejected by epidemiologists within the Agency as well as by two internationally recognized authorities in the field. During December 1988 and January 1989, SEU enrolled about 300 women in their survey, each of whom was paid $10 to participate. During this time, 12,000 to 14,000 women began new therapy with Accutane for an enrollment rate below 3% of eligible women. As was communicated to the sponsor by telephone in late November, results from this survey will be totally unreliable and biased against finding a problem. The results cannot be trusted and should be ignored in decision making about the future of Accutane.

Although argument can be made that the full package of interventions were not yet in place, several points should be considered. The most important aspects of the intervention went into place very quickly. Physician education was achieved almost immediately at the time of the April 1988 advisory committee meeting, and afterwards by editorials in professional journals and newspapers. The Pregnancy Prevention Kit was also quickly disseminated. The other major intervention, blister packs, apparently has not yet been introduced. However, blister packs will not affect physician prescribing and so their absence from the market in 1988 has no bearing on interpretation of usage data, which is really a measure of physician prescribing, or on the impact of this prescribing in terms of numbers of pregnancy exposures which occurred.

Conclusion

Accutane continues to be widely over-prescribed in both men and women. Pregnancy exposure to Accutane also continues at a high rate and the sponsor has not submitted a postmarketing study to assess the effect of interventions which is scientifically trustworthy or acceptable. Rather, the sponsor has proceeded with a survey effort which is fundamentally flawed and which has been repeatedly rejected by FDA and non-government experts.

FDA interventions have failed to achieve their primary objectives. There is no reasonable basis to expect that these objectives can or will be achieved in the forseeable future.

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Concur: _____ Chief, Epidemiology Branch and member, AMG

cc:
Nelson (HFD-502)
Evans/Huene/Bostwick (HFD-520)
Faich/Anello (HFD-700)
Stadel/Graham (HFD-733)
NDA # 18-662
DRU 1.7 Isotretinoin (Accutane)