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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: Overview of the First Year Evaluation of the Isotretinoin Risk Management Program

EXECUTIVE SUMMARY

The Divisions of Drug Risk Evaluation (DDRE) and Surveillance, Research, and Communication Support (DSRCS) in the Office of Drug Safety have prepared a set of reviews for assessing the enhanced Isotretinoin Risk Management Program (RMP) to prevent fetal exposure to isotretinoin following the first year of its implementation. The Isotretinoin RMP was initiated by Hoffmann-La Roche, Inc. with a transition period in January 2002 and became mandatory on April 10, 2002. The program which pertains to the Accutane-brand of isotretinoin is entitled the System to Manage Accutane-Related Teratogenicity® (S.M.A.R.T. ®)¹. The sponsors of the generic isotretinoin products implemented programs with identical components on their approval in late 2002 and early 2003. The analyses presented are based upon data supplied by Hoffmann-La Roche, contractors, and data resources available to the Food and Drug Administration's Center for Drug Evaluation and Research.

This group of evaluations of the first year of the Isotretinoin RMP includes (as below) analyses of spontaneous reports of pregnancy exposures, isotretinoin utilization during the year prior to and the year following the implementation of the RMP, as well as analyses of the Prescription Compliance Survey (PCS) and the Isotretinoin Patient Surveys, the two primary sources of assessing the RMP's tools.

¹ Throughout this set of reviews the Isotretinoin RMP may be referred to as SMART. For a more complete listing of terms used throughout this document, see Appendix 9, pg 103.

Pregnancy Exposures

Despite a modest reduction in isotretinoin prescriptions in the first year following implementation of the RMP, we identified similar numbers of pregnancy exposures during the Pre-RMP year and during the year following the implementation of the RMP (127 and 120 cases for Pre-RMP and Post-RMP periods, respectively). Pregnancies occurred throughout isotretinoin treatment for both Pre-RMP and Post-RMP periods with slightly more pregnancies occurring during the first month of therapy. Although, the number of women who were already pregnant prior to initiating therapy with isotretinoin decreased slightly during the Post-RMP period relative to the Pre-RMP period, there has been no improvement in baseline pregnancy testing, pregnancy testing during (monthly) isotretinoin therapy, or birth control methods among patients who became pregnant during the Pre-RMP period versus the Post-RMP period.

Despite the implementation of the Isotretinoin RMP, the actual reason that the pregnancies occurred often could not be delineated from the cases in the series. Nonetheless, some common themes were identified and could account for the pregnancy exposures. One of these entails compliance (or non-compliance) with labeled birth control recommendations. Many pregnancy cases reported either no contraceptive use, use of only one method of contraception, or non-compliance with the chosen method of birth control. We also found that labeled recommendations for baseline pregnancy testing among patients who were pregnant prior to starting isotretinoin, were not followed. Only about 10% reported a baseline pregnancy test during the last menstrual period (LMP) and none started isotretinoin within two weeks of their LMP. Although the label does not instruct to start within a specified period of time around the LMP, it does state that the baseline pregnancy test should be conducted during the first five days of menses immediately preceding isotretinoin therapy, and that the prescription for isotretinoin should be dispensed within 7 days of the “qualification date” or confirmatory pregnancy test. We also noted that a small number of women took isotretinoin without medical supervision.

It is important to keep in mind that since these analyses are based on data from spontaneous reports, they are subject to reporting bias. It is possible that there was an increase in the reporting of pregnancies in the Post-RMP year, due to publicity around the implementation of the RMP. Additionally spontaneous reports are variable in quality and completeness; as such, lack of information does not necessarily indicate lack of compliance with the RMP. Furthermore, experience of pregnancy failures may not represent general experience of isotretinoin users.

Isotretinoin Utilization

The number of isotretinoin prescriptions declined roughly 23% in the year following SMART compared to the previous year, suggesting that the SMART program may have influenced the number of isotretinoin prescriptions dispensed. Refill prescriptions also declined from 16.0% of all isotretinoin prescriptions in the year before SMART to 2.4% in the post-SMART year.

SMART appeared to have had little impact on other utilization variables such as prescribing physician specialty and patient age and gender. In the year prior to SMART, 76% of the prescriptions dispensed were written by dermatologists, similar to the proportion in the 12 months following SMART (80%). Females accounted for approximately one-half of the

isotretinoin claims in both the pre- and post-SMART eras. The majority of isotretinoin claims were from persons aged 16-29 years who accounted for 58.5% of the isotretinoin prescription claims in the year before SMART, and 59.5% of the prescriptions in the year following SMART. The results of these data are similar to the utilization data analyses reported by Hoffmann-La Roche.

Prescription Compliance Survey

The primary purpose of the Prescription Compliance Survey (PCS) is to measure compliance with the isotretinoin qualification stickers using a survey of pharmacies. In addition to compliance with the sticker program, the PCS also attempts to measure the completeness and accuracy of stickers from prescriptions filled at U.S. pharmacies. In conjunction with the survey, an audit of a sampling of pharmacies is being conducted to validate the main survey results.

The results show a very high rate of sticker use with prescriptions, which consistently exceed the primary objective of 90% complete and correct prescriptions. Results were consistent across gender, payer type, and age. There were minor differences in the pharmacy strata, specifically for prescription volume and population density. There do not appear to be any differences in the percentage of female patients across the survey waves, nor were there trends by age or payment type.

While the audit also shows a high rate of compliance and completeness among the validated prescriptions, the recruiting method appears not to be random, an important departure from the study design. Since the sponsor does not describe the implemented recruiting method at all, the utility and/or applicability of these data are questionable.

The two major limitations of the overall PCS are the low pharmacy response rate, and the low number of prescriptions captured for analysis. Although more than 750 pharmacies were recruited for each wave of the audit survey, there have not been 750 responses to date. In addition, during the third wave of the study, four pharmacy chains (Walgreens, CVS, Eckerd, and Rite Aid) and one retailer (Wal-Mart) asked to be removed from the study. These stores represent some of the largest pharmacy chains and pharmacy retailers in the U.S, and their removal may have compromised the ability of the PCS to obtain the necessary number of prescriptions for a valid analysis.

Overall, these serious problems in the survey implementation and response rate make it unclear if the survey is truly representative of the national picture, or if it is even achieving the stated objective of measuring sticker compliance. In addition, the implementation of the data validation audit appears to differ significantly from the analysis plan, making its interpretation and usefulness questionable.

It is important to remember that the PCS is an indirect measure of physician compliance with the Isotretinoin Risk Management Program. The pharmacies are middlemen, and unless the corporate, chain, or insurance reimbursement policy dictates compliance with the RMP, pharmacies can dispense isotretinoin without the sticker. In addition, the pharmacies can only influence physician compliance or participation by refusing to fill prescriptions not meeting

SMART requirements. Finally, given that this is an indirect measure of physician compliance, without directly asking doctors to confirm their level of participation in various sticker-associated practices, a high compliance percentage can be a misleading indicator of physician compliance.

Isotretinoin Patient Surveys

The Isotretinoin Patient Surveys are questionnaires designed to evaluate pregnancy prevention in isotretinoin treated women. The questionnaires in these surveys have recently been modified to incorporate questions specifically designed to measure compliance with the enhanced Isotretinoin RMP. These modified instruments incorporate RMP-specific metrics (e.g., presence of a prescription qualification sticker). The results of the patient surveys should be considered with extreme caution due to possible error from the following observations and inferences: low enrollment rate, recall bias, social desirability bias, bias due to both unit non-response and item non-response, and poor questionnaire design.

Absolute participation in the patient surveys increased from 16% - 19% in the year before SMART to 22%-26% in the first year of SMART. Although this represents an increase, it falls short of the 60% enrollment projected by the sponsor. Ninety-two percent of survey participants reported that they received a prescription with an isotretinoin qualification sticker, findings consistent with those of PCS and PCS audit.

Analyses of other components of the RMP were also conducted. In DDRE analyses of the Degge/SI cohort, 76% of survey participants reported they signed two consent forms and 81% reported the presence of a medication guide.

Analyses of both Slone and Degge/SI shows some improvement in the rate of any pregnancy testing, however only about 68% of apparently fertile and sexually active women reported two pregnancy tests prior to initiation of isotretinoin, a labeled requirement for therapy. Of menstruating, apparently fertile sexually active women, only 28% had a pregnancy test within the first 5 days of their menstrual period immediately before starting isotretinoin.

In DDRE analyses of the Degge/SI cohort, 4.2% of apparently fertile and sexually active 15-45 year-old participants reported no form of birth control. In total, 46.4% of apparently fertile and sexually active 15-45 year-old participants reported use of “appropriate” birth control consisting of two methods, at least one of which is a “primary” birth control method (e.g., oral contraception).

The presence of a prescription qualification sticker correlated highly but incompletely with performance of the pregnancy test. Overall 9% of Survey participants who reported a qualification sticker was present also indicated a pregnancy test was not done. Pregnancy testing was generally high both in the presence of a sticker (91%) and in the absence of a sticker (90%) for apparently fertile, 15 to 45 year old survey participants.

Among sexually active, apparently fertile 15 to 45 year old Survey participants, any birth control was noted in 97% of enrollees with a sticker and 96% of enrollees without a sticker.

Based on DDRE analyses, the Degge/SI dataset contains 15 reports of pregnancy among 4277 women on their first-course of isotretinoin therapy. The observed pregnancy rate for first-course users within the Degge/SI cohort is thus $15/4277 = 3.5/1000$. Since this rate is censored, it likely represents an underestimate of the rate realized when all these Survey participants complete follow-up. The reviewers have stated that this rate is virtually identical to the rate as reported by researchers from the Slone Epidemiology Group pre-RMP Accutane survey cohort of 2.9 per 1,000 women. Despite this observation, the value of a comparative analysis in the review of the patient surveys is called into question. Evaluation of the isotretinoin RMP is most appropriately based on patients' experience with all isotretinoin products and should not be confined to any subset of manufacturers, such as the innovator in this instance. Furthermore, in the analysis of pregnancy rates, the representativeness and comparability of these two cohorts is questionable because of differences in the survey instruments, financial incentives for participating, response rates, and the demographic composition of respondents and their treating physician specialties. We note from the review by Karwoski and Pitts that pregnancies reported by survey respondents are a minority of all reported pregnancies to FDA, and that the contribution of these reports changed from 20% in the pre-RMP period to 27% in the post-RMP period. Lastly, the post-RMP "rate" in the attached review does not take person-time exposure into account, nor the shortened patient exposure in the post-RMP period compared to the pre-RMP data other than to describe the latter factor non-quantitatively as "censoring." Notwithstanding these reservations about the cross-survey comparison and quantification of pregnancies, we note with concern the reports of continued pregnancies in the post-RMP survey.

CONCLUSIONS

The number of pregnancy exposures to isotretinoin has not decreased appreciably and may have increased relative to the overall decrease in use of isotretinoin in the year following the implementation of the enhanced Isotretinoin Risk Management Program. Our review of a number of parameters comparing the Pre-RMP to the Post-RMP pregnancy exposures suggest minimal or no improvement with the implementation of the RMP. However, it should be emphasized that benchmarks of success of the program based on pre-specified metrics were not defined and that experience of pregnancy failures may not represent general experience of isotretinoin users.

An important element of the enhanced risk management program is the use by physicians of stickers on the prescription representing their certification that the key elements of the program such as education, informed consent and, in particular, pregnancy testing have been performed and certified as negative. Data from pharmacies corroborated by patients indicate that well over 90% of dispensed prescriptions contain the sticker.

In judging how well the use of the sticker corresponds with pregnancy testing, we noted that among all women who reported receiving a prescription with a sticker, 91% reported a pregnancy test. Of note is that 9% with a sticker indicated that they had not received a pregnancy test. For the year prior to this enhanced risk management program, among apparently fertile, sexually active women, 74% reported having received pregnancy testing prior to initiation of therapy. In the year subsequent to this program, 91% reported such pregnancy testing.

Finally, during this latter period of enhanced risk management, 70% of women used some form of birth control although only 25% over all used contraception consistent with the label which requires two forms of birth control of which one must be “primary” such as the use of an oral contraceptive.

In summary, it appears that no substantial improvement has occurred in reported pregnancy exposures after implementation of the Isotretinoin RMP. Moreover, analysis of patient recall surveys reveals that qualification stickers have been issued by prescribing physicians to some patients who have not undergone pregnancy testing. Therefore, modifications in risk management to further reduce the likelihood of isotretinoin exposure during pregnancy should be considered at this time.

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BACKGROUND

Regulatory History

Isotretinoin (Accutane®) was first approved in the U.S. in 1982 and is indicated to treat the most serious form of acne. This form of acne is painful, permanently disfiguring, and does not respond to other acne treatments. Isotretinoin is very effective, but its use carries significant potential risks, including birth defects and even fetal death.

Because of Isotretinoin's potent teratogenic risks, the sponsor designed and implemented the Accutane Pregnancy Prevention Program (PPP) in 1988. The goal of that program was to minimize the risk of patients becoming pregnant while taking isotretinoin and so avoid exposure during pregnancy. Continuing pregnancies and a review of the PPP in 2000 revealing substantial non-compliance with critical elements of the program, led the Agency and the Dermatologic and Ophthalmic Advisory Committee to conclude that PPP had not been sufficiently effective in minimizing pregnancy exposure during isotretinoin treatment and that better alternatives were needed.

The new risk management program was developed by Roche and was approved as part of a labeling supplement on October 30, 2001. The program, entitled the System to Manage Accutane-Related Teratogenicity® (S.M.A.R.T. ®), was initiated with a transition period in January 2002 and became mandatory on April 10, 2002.

On November 8, 2002, the first generic version of Isotretinoin was approved (Amnestein®, Genpharm, Inc.). Two additional generic Isotretinoin products have been approved since then (Claravis®, Barr Laboratories, Inc. and Sotret®, Ranbaxy Laboratories Limited). Each of the generic drug companies implemented risk management programs with identical components as a condition of their approval. These programs are known by the following names:

Company	Isotretinoin Risk Management Program Name
Genpharm, Inc.	System to Prevent Isotretinoin-Related Issues of Teratogenicity (S.P.I.R.I.T.)™
Barr Laboratories	Adverse Event Learning and Education Regarding Teratogenicity (A.L.E.R.T.)™
Ranbaxy Laboratories	Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity (I.M.P.A.R.T.)™

Risk Management Program Goals

The Isotretinoin Risk Management Program was developed to address the two main goals²:

- 1) No woman should begin isotretinoin therapy if she is pregnant, and
- 2) No pregnancies should occur while a woman is taking isotretinoin.

² Refer to correspondence to Hoffmann-La Roche, Inc., dated October 6, 2000 (re: NDA18-662, NDA 21-177)

Risk Management Program Tools

The information below describes the tools of the enhanced Isotretinoin Risk Management Program. The tools developed by the sponsor were designed to prompt or guide practitioners, pharmacists, and patients in the proper prescribing, dispensing, and use of isotretinoin to minimize the isotretinoin exposure during pregnancy. The source of the information below is based on Accutane® labeling, August 2003.

- The **prescriber** must obtain Isotretinoin Qualification Stickers. To obtain the stickers the prescriber must:
 - Read booklet entitled *SMART Guide to Best Practices*
 - Signed and returned the *Letter of Understanding* containing the prescriber checklist which signifies that he/she:
 - Is knowledgeable about the risk and severity of fetal injury/birth defects from isotretinoin
 - Knows how to diagnose and treat the various presentations of acne
 - Knows the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy
 - Has counseled the patient on the importance of avoiding pregnancy during isotretinoin and for 1 month after stopping isotretinoin or have referred for expert, detailed pregnancy prevention counseling.
 - Will use the RMP procedures throughout the isotretinoin treatment course including monthly pregnancy avoidance counseling, pregnancy testing, and use of the qualification stickers.
 - The qualification sticker also signifies that:
 - The female patient has had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription.
 - The first test is obtained by the prescriber
 - The second test should be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy. For patients with amenorrhea, 11 days after the last act of unprotected sexual intercourse (w/o using 2 effective forms of contraception).
 - Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. This test must be repeated every month prior to the female patient receiving each prescription.
- The **female patient** must:
 - Have selected and committed to use 2 forms of effective contraception simultaneously, at least one which must be a primary³ form unless abstinence is chosen or the patient has undergone a hysterectomy.

³ Primary methods of contraception: oral contraceptives, implantable hormones, injectable hormones, hormonal patch, intrauterine devices, hormonal vaginal contraceptive ring, sterilization (male, female)

- Sign a Patient Information/Consent form about Accutane and birth defects, in addition to the Consent Form that all patients should receive about other potentially serious risks.
- Be given the opportunity to enroll in the Isotretinoin Survey.
- The **pharmacist** will:
 - Dispense isotretinoin only upon presentation of a prescription with the special qualification sticker.
 - Dispense a maximum one-month supply of isotretinoin
 - Fill prescriptions only within seven days from the date of "qualification,"
 - Provide a Medication Guide for patients with each isotretinoin prescription.
 - Not fill requests for refills (i.e. more isotretinoin without a new prescription) and phoned-in prescriptions.

Evaluation of the RMP

To measure the effectiveness of the Isotretinoin Risk Management Program, the sponsors were asked to use several independent outcome assessment approaches. These include the Isotretinoin Survey, conducted by either the Slone Epidemiology Unit of Boston University School of Public Health or the Degge Group, Ltd, and S.I. International; and an independent survey and audit of pharmacies to assess the use of Isotretinoin Qualification Stickers by prescribers.

Although specific assessment metrics were not mandated in the RMP approval letter, several primary and secondary assessment metrics were discussed between Roche and FDA and are outlined in Roche's *1 Year Report on the S.M.A.R.T Program*⁴. The **planned** primary and secondary⁵ metrics include the following:

Isotretinoin Patient Survey

- Primary Metrics
 - The primary assessment metric proposed by Roche for the Accutane Survey was that 60% of female isotretinoin patients would be enrolled in the survey one year after the implementation of RMP.
 - Survey respondents would generally be representative of the reference population of isotretinoin female patients.
- Secondary Metrics
 - Publication(s) of results from the Accutane Survey results will be initiated starting 6 months after labeling change.
 - Percent of patients with recall of taking a pregnancy test.
 - Percent of patients with recall of the Qualification Sticker affixed to their Accutane prescription.
 - Percent of patients with recall of receiving a Medication Guide.
 - Percent of patients with recall of using two forms of safe and effective contraception.

⁴ Hoffmann-La Roche submission–General Correspondence: *1 Year Report on the SMART Program*, June 30, 2003

⁵ Numeric values vis-à-vis the Secondary Metrics for both the Isotretinoin Patient Survey and the Prescription Compliance Survey were not specified in the sponsor's submission.

- Percent of patients enrolling in the Accutane Survey via the physician office, Accutane Card, and by toll-free telephone number.

Prescription Compliance Survey

- Primary Metrics
 - 90% of all physicians will use the Accutane Qualification Stickers by one year after labeling change and close to 100% by two years after labeling change.
 - 90% of all physicians completely and correctly complete the Accutane QS by one year after labeling change and close to 100% by two years after labeling change.
 - 90% of all prescriptions are dispensed with a Medication Guide by one year after labeling change and close to 100% by two years after labeling change.
- Secondary Metrics
 - Produce Newsletters that will be sent to prescribers, pharmacists, Managed Care Organizations, and Pharmacy Benefits Managers and will be initiated starting 6 months after labeling change.
 - Percent of physicians using the Accutane Qualification Sticker
 - Percent of Accutane QS completed appropriately
 - Percent of pharmacies dispensing Accutane Medication Guides

The set of reviews that follow summarize ODS's evaluation of the effectiveness of the enhanced Isotretinoin Risk Management Program for the first year following its implementation. The analyses presented are based upon data supplied by Hoffmann-La Roche, Inc., contractors, and other internal and external data resources available to the Food and Drug Administration's Center for Drug Evaluation and Research.

This group of evaluations of the first year of the Isotretinoin RMP includes analyses of spontaneous reports of pregnancy exposures, isotretinoin utilization during the year prior to and the year following the implementation of the RMP, as well as analyses of the Prescription Compliance Survey (PCS) and the Isotretinoin Patient Surveys, the two primary sources of assessing the RMP's tools.