

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

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Subject: Overview of the 1st Year of the Isotretinoin Risk Management Program
 (RMP)

The attached Office of Drug Safety (ODS) review evaluates the impact of the enhanced post-marketing risk management program for isotretinoin since its implementation in April 2002. The review consists of four reports that address the following the topics:

- Pregnancy exposures and contraceptive use patterns
- Drug utilization patterns
- Implementation of the pharmacy sticker program
- Surveys of patient-reported compliance and outcomes

Summarized in this overview are the key findings of each report.

Pregnancy exposures

For the one-year period prior to the implementation of the risk management program (pre-RMP), 127 women with pregnancy exposures to isotretinoin were reported. For a comparable one-year period subsequent to its implementation (post-RMP) 120 such cases were reported. Prescriptions for isotretinoin declined during the post-RMP period (see below.)

In the pre-RMP period, 12 women were pregnant prior to the initiation of the therapy and 7 women in the post-RMP period; one pregnancy could not be dated precisely. The remaining pregnancies occurred following the initiation of therapy and were observed throughout the course of treatment both pre- and post-RMP. Incomplete or absent patient adherence to labeled birth control recommendations was observed among the pregnancy cases, including no contraceptive use, use of only one method of contraception, or non-compliance with the chosen method of birth control. When patients were pregnant prior

to starting isotretinoin, labeled recommendations for baseline pregnancy testing and initiation of use timed with menses were not followed in certain cases. Seven reported pregnancies occurred in women who took isotretinoin without medical supervision.

Drug utilization

The number of isotretinoin prescriptions dispensed declined 23% in the first year following the implementation of the enhanced program from 1.51 million to 1.16 million. Refill prescriptions decreased from 16% in the pre-RMP year to 2.4% in the post-RMP year.

Pharmacy sticker compliance survey

Surveys of pharmacies to determine compliance with the prescription sticker element of the risk management program found that the number of prescriptions filled used the qualification sticker consistently exceeded the primary objective of 90%. The survey had important limitations including a low pharmacy response rate and the failure of some large pharmacy chains to participate.

Patient surveys

Participation rates in patient surveys were 16-19% during the pre-RMP period compared to 22-26% post-RMP. Survey respondents differed in their age distribution and prescriber specialty profile from all females receiving isotretinoin prescriptions. These findings raise questions about the representativeness of survey respondents for all isotretinoin users.

For those participants assumed to be fertile¹ and sexually active ("at risk for pregnancy"), 91% reported at least one pregnancy test prior to initiation of therapy whereas 68% reported receiving two pregnancy tests prior to therapy. For the year prior to this enhanced risk management program, among sexually active women inferred to be fertile¹, 74% reported having received pregnancy testing prior to initiation of therapy.

Concerning the use of qualification stickers, 92% of survey participants reported receiving a prescription with a qualification sticker, in close agreement with the pharmacy sticker compliance survey results. Among survey participants who reported receiving a prescription with a qualification sticker, 9% reported they did not have a pregnancy test.

Regarding the use of birth control among sexually active women aged 15-45 years inferred to be fertile¹, 4.2% reported they did not use any means of birth control. Conversely, 95.8% used some form of birth control early in their isotretinoin treatment course; 46% used two forms of birth control of which one was considered primary.

¹Fertile was defined by ages greater than or equal to 15 years and less than or equal to 45 years, having an intact uterus, and being premenopausal.

Conclusion

Notwithstanding widespread use of the isotretinoin sticker by pharmacy and patient surveys, pregnancies on isotretinoin therapy continue to be reported in equivalent numbers to the preRMP period. Pregnancy testing at least once at the initiation of therapy improved postRMP, with performance of two tests ranging from 63 to 68% of survey respondents depending on the at-risk denominator used. Women who reported pregnancies to FDA indicated some level of confusion about the appropriate timing of pregnancy testing relative to menses and the initiation of therapy, possibly due to ambiguity in the labeled directions.

Only one year has passed since the implementation of enhanced efforts to manage the pregnancy risks of isotretinoin. The limited and incomplete data reported to date indicate that compliance with sticker use and refill restrictions is high, but that the absolute linkage of stickers with pregnancy testing is incomplete. According to patient surveys, contraceptive practices have improved, but high-risk behaviors around contraception (such as improper use or lack of use) continue to place a portion of women at risk of an isotretinoin-exposed pregnancy.