

Addendum to the January 25, 2004 Roche Advisory Committee Briefing Document

This Addendum Report is being submitted on behalf of all the FDA approved generic manufacturers and distributors of Isotretinoin Capsules to provide comments on the proposal for an enhanced risk management program for the prevention of pregnancy as outlined in the January 25, 2004 Roche Advisory Committee Briefing Document. Generic isotretinoin capsules were first introduced to the US market in December 2002. Today, there are three generic companies distributing a therapeutically equivalent (AB rated) version of isotretinoin capsules in addition to Roche's Accutane[®].

Product	Company	Risk Management Program	ANDA No.	Approval Date
Amnesteem [®]	Mylan/Bertek – Distributor Genpharm – Manufacturer	S.P.I.R.I.T. ¹	75-495	Nov. 2002
Sotret [®]	Ranbaxy Pharmaceuticals, Inc.	I.M.P.A.R.T. ²	76-041 76-503	December 2002 June 2003
Claravis [®]	Barr Laboratories	A.L.E.R.T. ³	76-135 76-356	April 2003 April 2003

¹System to Prevent Isotretinoin-Related Issues of Teratogenicity.

²Isotretinoin Medication Program Alerting you to the Risks of Teratogenicity.

³Adverse Event Learning and Education Regarding Teratogenicity.

As part of the FDA requirements for the approval of an ANDA for isotretinoin capsules, the generic product must have the same or equivalent labeling and risk management program as the innovator product. Therefore, all the generic products have risk management programs that are the same as Roche's S.M.A.R.T. program.

FDA called a meeting on December 10, 2003 of all manufacturers and distributors of isotretinoin capsules to discuss the Agency's findings and concerns with the current isotretinoin risk management program for the prevention of pregnancy. FDA informed the companies of the planned joint meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee on February 26 and 27, 2004 to discuss the effectiveness of the isotretinoin risk management program for the prevention of fetal exposure to Accutane and its generic equivalents, and consider whether changes to this isotretinoin risk management program would be appropriate. During the December 10th meeting, FDA suggested that, ideally, the companies should work together to develop a consensus proposal to enhance the current risk management program. They also strongly suggested that any proposal contain a plan for a single repository or registry for data collection to permit meaningful analysis of data (Note- there are currently two separate voluntary surveys that collect information on female patients being treated with isotretinoin. Roche maintains one survey, and the Slone Institute at Boston University maintains the other survey under contract by the generic companies.) FDA informed the companies that an industry proposal was due to the Agency on January 26, 2004 to assure adequate lead-time for FDA review and dissemination to Advisory Committee members. This proposal would then be presented at the Advisory Committee Meeting in February.

The Agency primarily focused on the fact that the absolute number of pregnancies reported the year prior to the initiation of the current S.M.A.R.T. Program and those reported during the first year after its full implementation were about the same. Because there is no way to determine the actual rate of pregnancies or to know how completely pregnancies were reported, it is not possible to determine whether the implementation of the S.M.A.R.T. risk management program resulted in increased pregnancy reporting or that the program failed to decrease the number of fetal exposures. However, at FDA's request, all of the generic companies and Roche agreed to discuss and propose enhancements to the current risk management program as a way to further reduce the potential for fetal exposure to isotretinoin.

Realizing that there was very little time for all the companies, the generics and Roche, to reach consensus, immediately following the FDA meeting, the companies met and agreed to work together to develop one proposal for submission to the Agency. Representatives of all companies met on two additional occasions to develop a single consensus proposal. During these meetings, the companies developed a unified program by reaching consensus on sixteen points creating the core concepts and processes for developing a foundation for the enhanced risk management program for the prevention of pregnancy (See Attachment 1). The key components of the enhanced risk management program are the following:

- Mandatory prescriber registration.
- Mandatory registration of all female patients receiving a prescription for isotretinoin.
- Prescriber attestation of patient education/qualification in the system for each isotretinoin prescription.
- Mandatory reporting to the system of the results of a pregnancy test (for female patients of childbearing potential) conducted by an accredited laboratory within an appropriate time frame.
- Mandatory use of a Qualification Sticker on each isotretinoin prescription (Note- sticker would designate male or female patient).
- Dispensing of isotretinoin to female patients only if a current negative pregnancy test (for females of child bearing potential) is recorded in the system and the system provides an appropriate authorization number prior to dispensing or for a male patient if the appropriate authorization sticker is affixed to the prescription.
- Requires the pharmacist to access the registry system to confirm an authorization to dispense the drug for each and every prescription for a female patient
- Mandatory identification of product.
- Centralized mechanism for reporting and follow-up of pregnancies.

On January 16, 2004, Roche, on behalf of all of the companies, sent a draft process flow diagram (See Attachment 2) and a high level description containing the sixteen consensus points for the proposed pregnancy risk management program (See Attachment 1) to the Agency. The companies and FDA participated in a teleconference on January 23, 2004 to discuss the Agency's comments on the consensus proposal. The primary comments from the Agency on the proposal focused on three issues:

- (1) Registration of male patients in addition to female patients versus only female patients;
- (2) Patient interaction with the educational and risk management evaluation component of the program; and

(3) A firmer link between the registry and the pharmacist - perhaps through pharmacy registration.

Immediately following the FDA/Company teleconference, the companies met via teleconference to discuss the Agency comments and determine next steps. Since the briefing document was due to be sent to FDA that day, there was inadequate time for the companies to discuss and reach consensus on how to address the Agency's January 23, 2004 comments. Because of this, Roche decided to submit a separate briefing document that included the original sixteen-point consensus proposal agreed to by all companies along with their own plan to address the three issues raised in the FDA teleconference.

All companies continue to support the 16-point consensus proposal as submitted to FDA on January 16, 2004; however, we have not yet reached consensus on how to address the three issues the FDA raised during the January 23, 2004 teleconference. The generic companies have taken these three issues under advisement and request that they be addressed at the advisory committee meeting in the context of the reason for the Agency's requested enhancements to the existing isotretinoin risk management program, i.e., the reduction of fetal exposure.