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# Electronic Mail Message

**Sensitivity:** COMPANY CONFIDENTIAL
**Date:** 20-Jun-2000 04:36pm
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**TO:** See Below
**Subject:** Accutane Advisory Committee Meeting, Aug 17&18, 2000: Preliminary Draft of Issues and Discussants

We met with Dr Woodcock on Thursday, June 15, late afternoon to discuss the various Accutane issues and to obtain advice on the development of the most appropriate advisory committee meeting structure and content. This memo is to bring everyone up to date on the overall development plan, but it is not an exhaustive account of all of the details.

We discussed the scheduling of the advisory committee (Aug 17&18) to occur in sufficient time before the due date (Oct 29, 2000) of the Accutane NF NDA to work out the details of new programs emerging from the advisory committee meeting.

There are issues that are general to both isotretinoin products, Accutane and the "New Formulation" (NF), currently under review (NDA 21-177). In addition, there may be generic isotretinoin products as early as late 2001 or early 2002. 9 studies done

The preliminary draft structure begins with issues general to systemic isotretinoin, and the specific issues relating to the NF follow. The concern that "voluntary" efforts on the part of Roche that are not embedded in labeling or explicit conditions of approval will not translate to generic isotretinoin is specific to the Pregnancy Prevention Program (PPP) and would be discussed in that context.

Issue #1. Potential Hormonal Contraceptive-Isotretinoin Interaction: Investigational Program

Key background points:

1. Accutane was approved in the 80's, and only 10 subjects were studied in a fairly insensitive assay. One of 10 had a positive signal while on OCs and Accutane.
2. Today the hormonal contraceptives have much less estrogen or none at all, the injectable and implantable types and some of the oral types are progestational agents only.
3. There are reports of women becoming pregnant while using hormonal contraceptives, including the parenteral type; however, whether this is consistent with the failure rate of the method or a signal of an adverse interaction cannot be determined.
4. Roche is currently conducting early studies in this program, which is projected to last over a year. Preliminary results JUST arrived, but have not yet been reviewed by Biopharm.

The discussion objectives:

1. Concurrence that overall investigational program is sound and sufficient.
2. Concurrence that timeline is reasonable. (The estimated program duration is lengthy in part because of the scarcity of human hepatocytes for the in vitro screening of the numerous progestional agents, some of which are active and some of which are prodrugs).
3. Concurrence that proposed labeling adequately addresses the uncertainty and cautions that the hormonal contraceptive must be supplemented by a second method. The Committee may have labeling suggestions here.

Roche would present the investigational program and the timelines. The clinical reviewer could present the proposed labeling and briefly discuss the intent. FDA Biopharm staff would be available at the table for comment. Dr Woodcock recommended adding Pharmaceutical Science Advisory Committee representation for this discussion.

Issue #2. Psychiatric Events.

Key background points:

1. There are postmarketing reports of a variety of psychiatric events, suicide attempts, and suicides associated with

Accutane.

2. We have current labeling that asks physicians to act prudently "as if" Accutane may be causal.

3. Bob Nelson (FDA alumnus) was contracted by Roche to review psychiatric events. His report was a "draft" which underwent further review by Roche's consulting psychiatrist.

4. In the NF NDA, there is also a signal of a possible relationship.

5. The sum total of the information about the causality of psychiatric events associated with systemic isotretinoin will not be considered conclusive by most analysts. However, most may agree that more needs to be known.

The discussion objectives:

1. Concurrence that more needs to be known.
2. Discussion of how best to study the question.

Roche would present the "Nelson Report" and their proposals (if any) for further investigation. The clinical reviewer may present the NF data set here as it relates to psychiatric events. The Neuropharm group would be available at the table for comment and to discuss how the question could be studied further. We are inviting an adolescent psychiatrist from the Psych Pharm AC, and Erick Turner is looking into which psychiatrists on the Neuro AC should be invited. OPDRA would be at the table and prepared to comment on the Nelson Report, the Jicks' study, and the OPDRA case analysis. OPDRA is considering Psychiatric Preventative Measures which could be added to labeling. OPDRA and Neuropharm may have specific suggestions on how to further study the association with psychiatric events (we need an Agency position on whether there is a need for additional information, but not necessarily a specific study design).

what does he mean by Psych Pharm AC? Is this addiction?

Issue #3. Teratogenicity and Prevention of Fetal Exposure

Key background points:

1. There is no doubt or debate that isotretinoin is a potent teratogen.
2. There is new evidence that infants born without obvious signs of retinoid fetal injury may subsequently suffer neurodevelopmental problems.
3. Roche believes the current PPP is working well and can be improved in a voluntary manner.
4. Pediatric groups and the CDC have concerns about the apparent asymmetry between the restricted distribution of thalidomide to a population less likely to become pregnant and the open and liberally promoted distribution to a population more likely to become pregnant.
5. Roche believes that the estimates of the effectiveness of the PPP from the voluntary registry are sufficient for mensuration.

The discussion objectives:

1. Is a more accurate assessment of the frequency of fetal exposure needed?
2. Should distribution of systemic isotretinoin (Accutane, NF, and generic) be restricted to physicians, pharmacists, and patients who comply with a comprehensive program to prevent fetal exposure?
3. Should the program be interventionist or simply reportable when noncompliance occurs?

Roche (probably Allen Mitchell) would present PPP and the proposed "improved" PPP. We need an FDA or Celgene speaker to discuss STEPS. Lissy Vega would present the performance characteristics of the new version of STEPS (STEPS-2) The CDC, teratologists, and others can address the new findings in retinoid teratology and epidemiologic signals. Women's Health, the Pregnancy registry Group, or other FDA groups may propose speaking briefly here. The AC would have representation beyond DODAC, e.g., Repro AC. Dr Woodcock asked that OPDRA (Anne Trontell and Julie Beitz) present to her at the next briefing several options for registries and distribution. The options could be presented as performance criteria of the methods, instead of structural details (which could be proposed by Roche). The evolution of the promotion of Accutane from the 80's to the present could be presented by DDMAC.

A mandatory registry could provide more information than prevention of fetal exposure, e.g., psychiatric events. Since there will be several nondermatologist Committee members, an overview of the product and its labeling may be helpful, esp., the most recent labeling changes.

Issue #4. NDA 21-177, Accutane, NF.

Key background points:

1. Accutane is to be taken with food, and the NF can be taken either fasting or with food and only once daily. Many derms dose Accutane once daily already, and fasting teenagers may not be particularly common.
2. Accutane NF may be less effective, encouraging even more off-label increases in dosing.
3. Dose-ranging is inadequate for both products.

4. Psychiatric signal (see Issue #2).
5. Reviews in Clinical and Biopharm are still in progress. No information yet on whether Cmax and/or AUC are different between the two products.

The discussion objectives:
1. Should the NF be approved, and, if so, should both products stay on the market?
2. Should dose-ranging studies be conducted? Before or after approval (Phase 4)?
3. Additional questions as reviews progress.

Dr Woodcock recommended that we consult with Jane Axelrad for wording to craft into the NF action letter that describes the conditions of approval as including the educational, distributive, and registry methods. This statement of conditions would then apply to generic versions of the NF.

Finally, we discussed that Roche would like to have a teleconference with Dr Woodcock to discuss the advisory committee. Roche believes that such an advisory committee meeting is not necessary. Dr Woodcock charged Mary Jean and me with calling Roche and conveying that 1) she believes an advisory committee meeting is warranted, and 2) when she returns after being away from the office she would have a teleconference with Roche.

Jon

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