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NDA 18-662
NDA 21-177

OCT 6 2000

Hoffmann-La Roche, Inc.
Attention: Russell Ellison, M.D.
Chief Medical Officer
Vice President, Medical Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Ellison:

Based on our assessment of the advice we received from the September 18 and 19, 2000 meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC or "the committee") regarding your product, Accutane (isotretinoin), the Center for Drug Evaluation and Research (CDER) requests the following actions be undertaken by you. These actions relate to the post-approval risk management program for Accutane and address primarily components related to (a) pregnancy prevention and (b) the psychiatric events temporally associated with Accutane. Please note that the review division will address approvability issues for pending NDA 21-177 in a separate letter as this NDA is currently under review.

RISK MANAGEMENT – PREGNANCY PREVENTION

The committee agreed unanimously, and we concur, with the following two primary risk management goals with respect to efforts to prevent pregnancy in association with Accutane usage:

- (1) no one should begin Accutane therapy if pregnant
- (2) no pregnancies should occur while on Accutane therapy

In order to achieve these risk management goals, the committee agreed, and we concur, with the following basic plan of action:

- (1) Roche should initiate a heightened educational program for each Accutane patient and /or parent/guardian (if the patient is under 18 years of age) that includes verifiable documented written informed consent by all patients and/or parent/guardian (if the patient is under 18 years of age), both male and female, prior to receiving Accutane. This informed consent document should not only detail possible risks to a fetus, but should also

make clear to patients and/or parent/guardian (if the patient is under 18 years of age) the type of acne for which Accutane has been approved by FDA.

- (2) Roche should initiate a program whereby there is complete registration of all patients, both male and female, receiving Accutane.
- (3) Roche should initiate a program whereby there is complete registration and certification of practitioners who prescribe Accutane.
- (4) Roche should initiate a comprehensive program to track and report to CDER all fetal exposures to Accutane and the outcomes of such exposures. Such a comprehensive program should include, as a part, a formal, mandatory pregnancy register.
- (5) Roche should initiate a comprehensive compliance program that would link dispensing of Accutane to female patients only upon verification of adequate pregnancy testing.

In order to assess the impact of this risk management program on meeting the stated risk management goals for Accutane, Roche should develop and implement a monitoring program that will facilitate, at a minimum on an annual basis, your and our assessment of progress towards meeting these risk management goals.

CDER is hereby requesting that Roche submit to CDER, by the end of October 2000, its **plans and timelines** for developing and implementing the above plan of action and assessment monitoring program. After submission, appropriate representatives from the review division, the Office of Drug Evaluation 5, and the Office of Post-marketing Drug Risk Assessment will be happy to meet with Roche for further discussion of your plans and timelines.

RISK MANAGEMENT - PSYCHIATRIC EVENTS

The committee agreed, and CDER concurs, that there is sufficient concern to justify more intensive risk management with regard to the psychiatric events associated temporally with Accutane. The committee agreed, and CDER concurs, that the present primary goals of this component of the Accutane risk management plan should be:

- (1) to assure that prescribers are fully aware of these psychiatric events,
- (2) to initiate a comprehensive research program to investigate further the nature, etiology, and strength of Accutane association of these psychiatric events.

In order to achieve these risk management goals, the committee agreed, and we concur, with the following basic plan of action:

- (1) Roche should add information regarding these psychiatric events to the informed consent document signed by patients and/or their

- parents/guardians (if the patient is under 18 years of age) prior to receipt of Accutane.
- (2) Roche should develop and distribute an enhanced prescriber educational program to further educate prescribers about these specific psychiatric events.
 - (3) Roche should initiate a comprehensive research program to investigate further and help clarify the relationship between Accutane use and psychiatric events. Such a research program should include, among other components, a retrospective epidemiological cohort study and a prospective controlled trial designed to address these specific issues.

In order to assess the impact of this risk management program on meeting these stated risk management goals for Accutane, Roche should develop and implement a monitoring program that will facilitate, at a minimum on an annual basis, your and our assessment of progress towards meeting these risk management goals.

CDER is hereby requesting that Roche submit to CDER, by the end of October 2000, its **plans and timelines** for developing and implementing the above plan of action and assessment monitoring program. After submission, appropriate representatives of the review division, the Office of Drug Evaluation 5, and the Office of Post-marketing Drug Risk Assessment will be happy to meet with you for further discussion of your plans and timelines.

RISK MANAGEMENT – MEDICATION GUIDE DEVELOPMENT and DISTRIBUTION

The committee agreed, and CDER concurs, that it is imperative that a Medication Guide, pursuant to 21 CFR Part 208, be developed and implemented as quickly as possible. This Medication Guide should, among others, address for patients the pregnancy and psychiatric concerns with Accutane use and the actions that patients can take to avoid them. With this letter, CDER is notifying Roche that, based on information from post-marketing experience, CDER has determined that Accutane poses a serious and significant public health concern. This concern requires development and distribution of a Medication Guide in order to assure safe and effective patient use of Accutane and to help prevent serious adverse events. In addition, CDER has determined that Accutane has serious risks relative to its benefits. Patient should be made aware because this information as it could affect patients' decisions to use, or continue to use, the product. Please see 21 CFR 208.1(c).

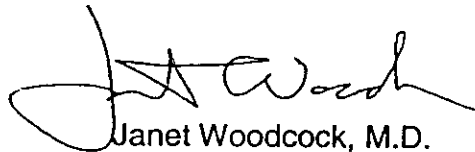
CDER, therefore, hereby requests that Roche submit, before the end of October 2000, a supplemental application to its approved NDA 18-662 that would include a proposed Medication Guide. The proposed Medication Guide should be formatted in two different ways and should comply with all Medication Guide regulatory parameters. One proposed Medication Guide should be formatted such that the Medication Guide is

incorporated into unit-of-use packaging as an integral part of the package. The second proposed Medication Guide should be formatted such that the Medication Guide would be a separate document that would be given to the patient by the dispensing pharmacist. After submission of this supplemental application, appropriate representatives of the review division, the Office of Drug Evaluation 5, the Office of Post-marketing Drug Risk Assessment, and the Division of Drug Marketing, Advertising, and Communications will be happy to meet with you for further discussion of your proposed Medication Guide.

We look forward to continued close cooperation with Roche in achieving the risk management goals outlined for this product.

If you have any questions concerning these requests or any other aspect of this letter, please call Indira Kumar, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

A handwritten signature in black ink, appearing to read "Janet Woodcock". The signature is fluid and cursive, with a large initial "J" and "W".

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

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Hoffmann-La Roche, Inc.

Attention: Russell Ellison, M.D.

Chief Medical Officer,

Vice President, Medical Affairs

340 Kingsland Street

- Nutley, New Jersey 07110-1199

Dear Dr. Ellison:

The Agency would like to outline and discuss the outcome of the September 18 and 19, 2000, Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) Meeting regarding Accutane (isotretinoin) (NDA 18-662, capsules and NDA 21-177, new formulation).

As discussed, the following DODAC recommendations were made and concurred by this Division regarding the post marketing risk management of Accutane, including programs to prevent pregnancy and the associated psychiatric events. Please note that the Division will address NDA 21-177, the new formulation, in a separate letter since this NDA is currently under review.

The Committee agreed unanimously with the following three goals as outlined by the Agency:

No one should begin Accutane® therapy if pregnant
No pregnancies should occur while on Accutane® therapy
Implementation of a monitoring program to assess the progress towards the above.

The Committee selected option number 3 to achieve the above stated goals while balancing the associated burdens. Option 3 requires:

Education and Informed Consent
Complete Participation (Registration of Patients and Physicians)
Tracking of Pregnancy Exposures (Pregnancy Registry, Surveys, External Data)
Optimal Compliance via Linkage (Pregnancy Testing)

The Committee agreed that there was sufficient concern to justify more risk management with regard to the associated psychiatric events. This includes implementation of a

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Medication Guide addressing psychiatric issues that would be required at the point of dispensing. The Committee reminded Roche that the current consent form did not include psychiatric effects and that the educational information should be enhanced to educate professionals of this concern.

The Committee also recommended that further studies be performed, such as, basic science research, an open cohort study (survey), a retrospective epidemiologic cohort study, and a prospective controlled trial to help clarify the relationship between Accutane® use and psychiatric events.

Under 21 CFR 314.102(e) of the new drug regulations, you may request a meeting with the Division to discuss any proposals that you may have to the above recommendations by DODAC and this Division.

If you have any questions, call Indira Kumar, Regulatory Project Manager, at (301) 827-2020.

Sincerely

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug

Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research

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cc:

Archival NDA 18-662

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HFD-540/Div. Files 18-662 & 21-177

HFD-540/I.Kumar/ M. J. Kozma-Fornaro

HFD-540/J. Wilkin/M. Okun/K. O'Connell

HFD-001/J. Woodcock

HFD-002/D. Murphy/L. Pauls

HFD-105/J. Bull/M. J. Walling

HFD-104/S. Kweder

HFD-430/Himmel/J. Beitz/A. Trontell/A. Vega/D. Wysowski/P. Guinn

HFD-120/R. Katz/Laughren/Turner

HFD-880/J. Lazor/D. Bashaw

HFD-42/N. Ostrove/K. Lechter/C. Roberts

HFD-21/K. Topper/ J. Tracey/Reedy/Henriquez

Drafted by: I. Kumar/September 21, 2000, 9-22-00 10:15am, 2:50pm

Initialed by: JW 9-21-00 5:00pm, JB 9-22-00 9:45am

Final:

Filename: NDA 18-662 & 21-177 Accutane AC to HLR 9-22-00

GENERAL CORRESPONDENCE (GC)