DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT FOR NDA 18-662 ACCUTANE® (isotretinoin) Capsules

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Executive Summary

Patients with severe recalcitrant nodular acne have benefited from the use of Accutane® (isotretinoin) since it was first marketed in 1982. Severe recalcitrant nodular acne is a disfiguring disease that can often result in significant permanent scarring. Patients with severe recalcitrant nodular acne who have failed topical and systemic antibiotic treatment have few alternative effective therapeutic modalities other than Accutane.

There is a comprehensive postmarketing risk assessment and management framework for Accutane based on the Roche Drug Safety pharmacovigilance program and the Pregnancy Prevention Program for Women on Accutane℠ (PPP), which was implemented in 1989 and modified in 1990. This framework was designed to not only define and evaluate the reported risks of isotretinoin, but also intervene to reduce those risks. Communication about risks and preventative strategies to prescribers and patients is a key part of this approach. The PPP has recently been updated to target new interventions at prescriber and patient behaviors that have been observed in those pregnancies that still occur. This has resulted in new labeling approved by FDA in May 2000 and communicated by a Dear Doctor letter sent to all known Accutane prescribers.

This risk management strategy defines how the topics in this Briefing Document are analyzed and addressed. The Briefing Document provides background information related to the safe use of Accutane for discussion at the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting. This Executive Summary highlights the analyses of and current activities for three specific topics: Pregnancy Prevention Program, Hormonal Contraceptive Evaluation Program, and Psychiatric Conditions.

Pregnancy Prevention Program

Preventing pregnancies in women prescribed Accutane, irrespective of outcome, is the absolute goal of the pregnancy prevention program. From the outset, the Accutane label has carried stringent warnings against its use during pregnancy. In July 1988, Roche implemented the Pregnancy Prevention Program for Women on Accutane, which was the first of its kind; the program was improved in 1990 based on data from the first year of this intervention. The PPP included elements such as a female patient informed consent form, a kit to help providers counsel patients, free referrals to a gynecologist for contraceptive counseling, and a requirement to use two forms of effective contraception simultaneously.

Since 1991, Accutane use has increased. In view of the evidence from prevalence studies of severe nodular acne, large standardized surveys of physicians, and data on actual prescribing practice from NHAMC and other databases, this increase does not suggest significant use outside the indicated population. Importantly, the number of pregnancy reports has not increased appreciably during this period of greater Accutane use. Evidence from three sources; the Accutane Survey conducted by the Slone Epidemiology Unit of 495,000 women using Accutane during this time, a recent pilot study of pregnancy rates from a UnitedHealthcare Research Database, and a large clinical trial, suggests that the PPP has reduced pregnancy rates in women prescribed Accutane by 80 to 90 percent from what would be expected from usual contraception

failure rates. For each 1000 women treated with Accutane, pregnancy has been prevented in about 996. However, while the pregnancy rate has decreased, the absolute number of pregnancies has not. In as much as contraception failure rates in an ideal situation can be as low as 0.1%, Roche is committed to a further substantial reduction in the risk of pregnancy in women prescribed Accutane.

A review of all data accumulated on Accutane exposed pregnancies has characterized the factors that keep a small percentage of women at risk. A consolidated and comprehensive strategy for changing high risk prescriber practices and patient behaviors to reduce pregnancies further in Accutane treated women has been developed and is being implemented as a Targeted Pregnancy Prevention Program (T-PPP), which is specifically based on these data. Balancing the likelihood of reducing the risk of pregnancy against risks to the current accomplishments of the PPP, the T-PPP presents the most effective way to further substantially reduce the risk of pregnancy. Key elements of this program were implemented beginning in June 2000.

The Accutane Survey conducted by the Slone Epidemiology Unit remains a key component in determining the pregnancy rate and monitoring the effectiveness of the T-PPP. The T-PPP will considerably increase the enrollment in the Accutane Survey will enable a more accurate assessment of the pregnancy rate and the patterns of contraceptive behavior. Ongoing collection and evaluation of this and other data will guide further PPP improvements. Roche is committed to ensuring that this and other metrics will have the desired effect of further reducing the rate of pregnancies in Accutane treated women.

Hormonal Contraceptives Evaluation Program

A comprehensive in vitro and in vivo risk assessment program is underway to confirm the lack of interaction between isotretinoin and its metabolites and hormonal contraceptives. No evidence of any interaction has been observed in the preliminary data. The studies will be submitted by the 4th quarter 2001.

Psychiatric Conditions

In consideration of the number of spontaneous reports of psychiatric conditions in association with Accutane therapy, Roche, in discussion with the FDA, amended its label to reflect this unverified signal in February 1998. To attempt to verify this signal, Roche initiated a multifaceted risk assessment whose cornerstone was a pharmacoepidemiological analysis of these reports. This analysis evaluated them within the context of the etiology and epidemiology of psychiatric conditions, including suicidal behavior. The report, which was submitted to the FDA in March 2000, found no evidence of an increased risk for psychiatric conditions associated with Accutane therapy. It concluded that psychiatric events reported in association with Accutane therapy reflect the multiple risk factors in the population of adolescent and young adults afflicted with the disfiguring disease of acne.

Several other analyses were undertaken, all of which similarly failed to identify any causal relationship between Accutane and psychiatric conditions in the spontaneous reports or other data

sources. An independent clinical review of all reports of suicide by an expert suicidologist found no evidence of a causal association with Accutane. An exploratory analysis of data from a large prospective clinical trial comparing two isotretinoin formulations showed no evidence of increased incidence of psychiatric morbidity using a validated screening instrument. In addition, an epidemiological analysis of other databases found no elevated relative risk of psychiatric conditions associated with Accutane, when compared to other acne therapies such as antibiotics. A review of the literature on retinoids and the central nervous system found no evidence of a plausible mechanism for psychiatric conditions in association with Accutane therapy.

Overall, these extensive analyses failed to verify the signal for increased risk for psychiatric adverse events in association with Accutane, which had been suggested by the number of spontaneous reports.