Appendix I.

Overview of Psychiatric Adverse Event Association with Isotretinoin

An understanding of causality in drug-associated adverse reactions is important for maximizing safe and effective use. Causal linkage between isotretinoin treatment and psychiatric events cannot be established from the observations in post-marketing reports due to under-reporting, the high background incidence of psychiatric illness in the population, and the incomplete nature of spontaneous reports. However, the observations available in the spontaneous reports and in the published literature provide signals for consideration in determining what measures should be taken in response to the reported events.

According to the sponsor, the number of domestic and foreign reports of *serious* adverse events in the post-marketing adverse event database for Accutane® as of April 30, 2000 was 5,665. Of the 28 organ system categories, the one with the largest percentage of *serious* reports is psychiatric (18.8%). The most recent Periodic Adverse Drug Event Report for Accutane® includes, for a *12-month period*, over 750 *new* psychiatric adverse event reports (foreign and domestic), including 200 coded as serious, 9 suicide attempts and 6 completed suicides.

The true number of cases is, of course, unknown since under-reporting of adverse events is significant. Under-reporting is exacerbated when the event has a high background rate and the drug has been marketed for many years. For events such as depression, reporting is probably further hampered by failure to recognize the diagnosis in many affected patients. On the other hand, spontaneous reports are entered into databases even if they contain no data suggesting a contribution of the drug to the reported adverse event.

The FDA performed an analysis of suicides and *hospitalized* cases of depression, suicidal ideation, and suicide attempts in U.S. patients on isotretinoin. The analysis included reports that had been entered into the FDA Adverse Event Reporting System (AERS) database from marketing to May 2000[1].

[1] Note that not all cases reported to the agency as of May 2000 had been entered into the database at the time of this analysis. Foreign cases were not analyzed even though they are included in the database.

There were 24 persons reported who committed suicide during, and 13 persons who committed suicide after, isotretinoin use. There were 85 persons reported who were hospitalized for depression, suicidal ideation, and/or suicide attempt during or shortly after isotretinoin use, and 25 persons reported hospitalized for these conditions after stopping isotretinoin. In total, there were 147 cases reported of suicide and hospitalized depression. Among these, 38% had a previous psychiatric history, 33% had none, and information was unknown for 29%.

Of the 37 individuals who committed suicide, 84% were male (31 of 37). The median age was 17 years. The median time from starting use of isotretinoin to suicide was about three months. Of the individuals who were hospitalized for depression, suicidal ideation and uncompleted suicide attempts, 56% were female. The median time from beginning use of isotretinoin to hospitalization was about one month, and some experienced persistent depression after isotretinoin was stopped. One person with unspecified previous history developed a psychotic depression and had a positive dechallenge with isotretinoin discontinuation, followed by a positive rechallenge when isotretinoin was restarted.

The number of *reported* suicide cases in the isotretinoin database for U.S. patients was about one-ninth the number of suicides predicted based on the 1998 U.S. age-specific suicide rate in 15-19 year olds. Because the extent of under-reporting is unknown and the usage data is an estimate it is not possible to say whether the total number of suicides in U.S. Accutane users exceeds the predicted number.

Reports that best inform adverse event assessment have substantive content and few or no confounders. Especially useful are such reports that document resolution of symptoms when the suspect drug is stopped, and recurrence when it is resumed (positive dechallenge and rechallenge). According to a consultant's report submitted by the sponsor, a majority of 344 mood disorder cases with substantive content had off-set of psychiatric symptoms within 30 days of stopping isotretinoin (foreign cases were included in this analysis). Most of those cases resolved within 15 days. Of the 25 cases that had *both* on-set and off-set within 15 days, 23 had resolution reported within 7 days. Of those 23 cases, off-set was reported to occur within 4 days for 17 cases

This finding is consistent with the agency's analysis of 28 cases of depression, mood disorder, and self-injurious behavior with positive dechallenge *and* positive rechallenge. The median time to onset of symptoms was 36 days with a median recovery period of 7 days. Improvement or resolution of symptoms occurred after discontinuation of Accutane®, Accutane treatment course completion, or dose reduction. Some patients required psychiatric intervention or antidepressant medications. Upon rechallenge, the median time to recurrence was 9 days with a median recovery period of 8 days.

These observations from spontaneous reports are also consistent with published cases. For example, Scheinman *et al* (1*)* reported depression in 7 of 700 patients with cystic acne, psoriasis, cutaneous disorders of keratinization, or basal cell carcinoma on isotretinoin therapy. The symptoms of depression resolved within 1 week of stopping therapy. One patient was rechallenged and symptoms recurred. Two of the seven patients had had previous Accutane® treatment without episodes of depression.

Hazen *et al* (2) reported that 6 of 110 patients with acne or keratinizing disorders experienced depressive symptoms while being treated with isotretinoin. One of these patients had a previous history of depression. Five patients continued on the drug despite the symptoms, which rapidly resolved upon discontinuation of the isotretinoin.

Offset after suspect drug discontinuation *in response to* the occurrence of depression may be biased by "power of suggestion". However, positive dechallenges are observed in the spontaneous reports after isotretinoin is stopped upon completion of the acne treatment course, as opposed to discontinuation in response to the psychiatric event. It has been hypothesized that resolution of clinical *depression* at completion of Accutane® therapy reflects improved appearance, but data supporting this hypothesis are not conclusive. (3, 4)

The AERS database also includes reports documenting negative dechallenge. Analysis of the 85 cases hospitalized for depression, suicidal ideation or suicide attempts showed that 18% had persistent problems after isotretinoin discontinuation.

Another type of evidence helpful in causality assessment is the occurrence of the event with administration of pharmacologically distinct substances that bind to the same physiologic receptors. Symptoms similar to those seen in Accutane® reports (depression, mood swings, insomnia, fatigue, headache, aggressive behavior, irritability, and/or uncontrollable crying) have been documented in association with high-dose vitamin A, and with etretinate, a systemic retinoid used in severe psoriasis. In 1972, Restak (5) described the development of a severe neuropsychiatric reaction to chronic high dose vitamin A in an 18 year-old acne patient who had no antecedent psychiatric illness. In this case, severe depression preceded the development of pseudotumor cerebri. Resolution of both effects occurred rapidly upon discontinuation of the vitamin A (pseudotumor cerebri is also a well-documented adverse effect of the synthetic retinoids). Another report describes depression in a 54 year old with no prior psychiatric history who had ingested twelve times the recommended daily allowance of

vitamin A for 2 years. Full recovery occurred within 2 months of stopping the vitamin supplement (6).

Pharmacologic plausibility is also supported when there is evidence of a dose response. There are two published cases (7, 8) that suggest etretinate-associated psychiatric events *might be* dose dependent. There are a number of Accutane® cases that also suggest a dose effect. However, a dose threshold *cannot* be ascertained from spontaneous reports or published cases because of incomplete information and/or bias introduced when dosage is decreased *in response to* depression.

Biologic plausibility is another type of information that can inform adverse event assessment. This does not require knowledge of a mechanism of action for the putative association, but rather an examination of whether the association is biologically "feasible", given the available science.

The effects of isotretinoin on fetal brain development have been extensively studied, but little is known about functional effects of isotretinoin on the adult brain. There is, however, substantial information about retinoic acid and the adult central nervous system. It is known that retinoids, including isotretinoin (8), enter the central nervous system, and that retinoid receptors are present in adult brain. Data linking retinoids with regulation of neuronal pathways thought to be involved in mood and thought are also emerging. For example, retinoid receptor mutant mice have impaired dopamine signaling (9). Retinoic acid may also be involved in regulation of a brain signal transducer called MARCKS (myristolated alanine-rich C kinase substrate). Specifically, it has been reported that retinoic acid down-regulates expression of MARCKS in a dose-dependent manner in immortalized hippocampal cells, and there is accumulating evidence that MARCKS is a primary target of long-term lithium treatment (10). The clinical importance, if any, of these examples is unknown, but they serve to illustrate that retinoid effects on neuropsychiatric function are not biologically implausible.

CONCLUSION

None of these elements of evidence, or their totality, allows a determination as to whether isotretinoin *causes* psychiatric morbidity. Warnings about serious adverse events associated with drugs are not dependent on proof of causality, and the manufacturer of Accutane® has incorporated a warning into the labeling based on the inconclusive evidence. The question before the agency is whether the current labeling is an adequate risk management strategy given the available information.

Options for Risk-Management

The options for risk management in this situation must be considered in the context of the substantial benefits of the drug and the population in which it is used. Specifically, Accutane® is uniquely and highly effective for the most severe form of acne, which if not adequately treated causes significant and often permanent disfigurement. In many cases a single 16-20 week treatment course is *curative*.

At the same time, the population for whom Accutane® is prescribed is overwhelmingly young and healthy. Accutane® has been associated with many adverse events affecting nearly every organ system, and is a potent teratogen. Some of these adverse events are serious/life-threatening and the current labeling includes a Black Box Warning, 11 additional Warnings, and 18 Precautions.

Two options for risk management are:

1) Maintain the current labeled Warning
2) Implement elements of risk management in addition to those accomplished by the sponsor and the Agency to date

RISK-MANAGEMENT ELEMENTS FOR CONSIDERATION:

1. Education/Intervention

- Professional continuing education programs for prescribers/health care providers
- Informed Consent
- Directed assessment during treatment

2. Labeling Change

- Constrained by absence of data (risk factors, dose, etc)
- Interim labeling: active monitoring, description of symptoms, advice about drug discontinuation…
- Patient Information Brochure – *Optional* use; the current Brochure is under revision

- Medication Guide for Patients – *Required* distribution of easy-to-understand information

3. Formal Studies

    - Prospective controlled trial designed to determine causality or lack thereof
    - Large open cohort studies aimed at better characterizing psychiatric events and generating hypotheses for controlled trials
    - An adequately powered, well-designed retrospective epidemiologic cohort study
    - Basic science research to improve knowledge base about the effects of isotretinoin on the central nervous system
    - Other

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