Joint Meeting of the
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)
and the
Drug Safety and Risk Management Advisory Committee (DSaRM)

July 12, 2004
8 am – 5:30 pm
ACS Conference Room, 5630 Fishers Lane, Rockville, MD

Minutes

DODAC
Robert S. Stern, M.D. (Chair)
Roselyn E. Epps, M.D.
Robert Katz, M.D.
Sharon S. Raimer, M.D.
Eileen W. Ringel, M.D.
Jimmy D. Schmidt, M.D.
Michael G. Wilkerson, M.D.

DODAC Consumer Representative
Paula Knudson

DSARM
Ruth S. Day, Ph.D.
Curt D. Furberg, M.D., Ph.D.
Jacqueline S. Gardner, Ph.D., M.P.H.
Eric S. Holmboe, M.D.
Robyn S. Shapiro, J.D.

DSARM Consumer Representative
Arthur A. Levin, M.P.H.

Industry Representative
None in Attendance

Executive Secretary
Kimberly Littleton Topper, M.S.

Consultants
Margaret Honein, Ph.D., M.P.H.
Sarah Sellers, Pharm.D.

FDA Participants
Jonca Bull, M.D.
Denise Cook, M.D.
Tapash Ghosh, Ph.D.
Shiowjen Lee, Ph.D.
Jill Lindstrom, M.D.
Marilyn Pitts, Pharm.D.
Anne Trontell, M.D., M.P.H.
Jonathan Wilkin, M.D.
Jiaqin Yao, Ph.D.

I certify that I was at the June 12, 2004, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) and these minutes accurately reflect the discussions of the committee.

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Robert S. Stern, M.D.,
Chairman, DODAC

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Kimberly Littleton Topper, M.S.
Executive Secretary, DODAC

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Minutes

The meeting was called to order at 8:00 by Dr. Robert Stern. He welcomed everyone and had the head table introduce themselves. The conflict of interest statement was read into the record by Kimberly L. Topper. Dr Jonca Bull welcomed everyone and thanked the committee for assisting the FDA in their deliberations. She reminded the committee of the February 04 discussions on fetal exposure and the proposed Risk Management Plan (RMP) Dr. Jonathan Wilkin also thanked the committee and set the stage for discussions on (NDA) 21-701, proposed trade name Tazoral (oral tazarotene 1.5mg and 4.5 mg) capsules, Allergan, Inc., proposed for the treatment of moderate to severe psoriasis, including risk management options to prevent fetal exposure. He reminded the committee that no product is perfect and finding the balance for the risk benefit ratio is what they need to look for during the day's discussions.

Denise Cook, M.D., FDA, provided an "Introduction to Psoriasis & The State of the Armamentarium." She discussed the prevalence, the genetics and pathogenesis, and the clinical variants of psoriasis. She presented the current treatments available and the side effects and contraindications of each.

Allergan NDA Presentation

Patricia Walker, M.D., Ph.D., Vice President, Skin Care Pharmaceuticals, Allergan, Inc. introduced Tazarotene Capsules in the treatment of psoriasis. She reminded the committee that Allergan is seeking the approval of Tazarotene for the treatment of moderate to very severe plaque psoriasis. She discussed the regulatory history of Tazarotene and provided a list of the members that were available to answer the committee questions.

Alan Menter, M.D., Clinical Professor of Dermatology, University of Texas, Southwestern, presented on Psoriasis: Disease Overview and Treatment Options. He stated the opportunities to improve care exist and that psoriasis is a diverse disease and no one drug is suitable for all patients. Current treatments have therapeutic limitations and a full range of safe, efficacious and accessible medications are needed for the psoriatic population.

Patricia Walker, M.D., Ph.D. presented the pharmacology of Tazarotene. Tazarotene is a prodrug with only one active metabolite, tazarotenic acid. It is an acetylenic retinoid and has a locked molecule. She then covered the efficacy data for Tazarotene. The safety and efficacy of oral tazarotene is based on the results of 12 phase 1 studies in normal volunteers, 1 dose ranging study in patients with moderate to very severe plaque psoriasis and 4 phase 3 studies in patients with moderate to very severe plaque psoriasis. The Overall Lesional Assessment (OLA) was an integrated clinical assessment of overall psoriasis severity and it evaluates the signs of psoriasis on a 6 point scale (none, minimal, mild, moderate, severe and very severe). A photo numeric guideline was provided for clinical evaluation. She provided examples of clinical response and the demographic breakdown of the clinical trials. The efficacy summary showed that `20% of patients achieved no or minimal disease, moderate (>50%) to complete clearing was achieved in the majority of patients, significant improvements in plaque elevation, erythema, scaling, purities, and % body surface area (BSA), maintenance of benefit was observed following discontinuation of drug, there was no rebounding and a large portion of patients (79%) expressed treatment satisfaction. She ten discussed the clinical development safety data. The bone mineral density (BMD) changes were small with individuals with gains or losses of $\geq$5% within expected variation and they were not associated with fractures, osteoporosis, age, gender or systemic corticosteroids. She stated that they did not

recommend routine laboratory evaluations nor was routine bone monitoring necessary. She then explained the proposed RiskMap for oral Tazarotene. She stated their goals as 1) women who are pregnant shall not be prescribed or dispensed oral tazarotene and 2) women taking oral tazarotene shall not become pregnant. The primary components of the RiskMap will be mandatory registration for all patients, targeted education for all patients, mandatory registration and certification of physicians and pharmacies, verification of all patients qualified by pharmacist through interaction with technology-based system, laboratory based pregnancy testing system, managed access, pregnancy exposure registry, and program effective metrics.

Alan Menter, M.D. then discussed the Risk Benefit Assessment. He discussed the important differentiating characteristics of oral tazarotene and the characteristic safety profile of systemic retinoid drugs. He stated that the half-life of the drug is very short; it can be taken when patient drinks alcohol, there is neither change in the lipid metabolism nor a change in the hepatotoxicity and the alopecia is not different after 12 weeks and the mucocutaneous reactions are mostly mild. He concluded that oral tazarotene is safe and effective and they have shown sustained clinical benefit in patients with moderate to very severe plaque psoriasis; ongoing therapy with tazarotene capsules provides extended benefit; there is a high rate of patient acceptance and a low dropout rate due to adverse events. He concluded that "Based on the efficacy and safety profile, tazarotene capsules should be available as an option for ALL patients, male and female, with moderate to very severe plaque psoriasis." Allergan then answered clarifying questions from the committee.

The committee took a 15 minute break.

FDA Presentation

Jiaqin Yao, Ph.D., FDA, presented the "Toxicology Studies of Tazarotene." He discussed the toxicity in fertility and early embryonic development, prenatal and postnatal development, male reproductive toxicity, the recommended human dose and the lowest teratogenic dose. He concluded that the human may be the most sensitive species for teratogenicity of retinoids; tazarotene is a more potent Teratogen than other retinoids in rats and rabbits on an mg/kg/day basis; and tazarotene is a probable human teratogen.

Tapash Ghosh, Ph.D. FDA, presented "Clinical Pharmacology & Biopharmaceutics" covering pharmacokinetics of Tazarotene (TAZ) and Tazarotenic acid (TA) in humans; the potential for drug-drug interactions and the tazarotenic acid in semen. He concluded that the no-effect limit for teratogenicity for TAZ/TA is unknown in humans; the fertilized egg may remain exposed to TA in the semen following repeated sexual encounters; and the risk to the fetus, if any, while a male patient is taking the drug or after it is discontinued can not be ruled out.

Denise Cook, M.D., FDA, discussed the clinical safety of oral tazarotene. She covered the safety discontinuations, the adverse events that led to discontinuation in the long term trial, the significant adverse events to include the bone, metabolic and endocrine events, and the long term safety trial. She concluded that for the neuropsychiatric events there was no difference between tazarotene and placebo in the controlled trials but due to the limitations of the metrics employed and the statistical power an association cannot be ruled out, given the existing concerns about other such effects from other retinoids. She also stated that there was a mean bone mineral density (BMD) decrease over time for the entire set of patients, with some having decreases close to 30%.

Shiowjen Lee, Ph.D., FDA, provided the "Biostatistical Analysis of Pivotal Studies." She stated that oral tazarotene is statistically superior to placebo regarding treatment success although success rates are below 20% for both studies; female patients had higher success rates than males though makes accounted for over 2/3 of study enrollment in each trial. Treatment success decreases as baseline OLA score increases and there is insufficient data to evaluate the efficacy claim of "very severe" plaque psoriasis. Oral tazarotene demonstrates short term efficacy in treating scalp psoriasis but not in treating nail psoriasis.

Denise Cook, M.D. then presented the clinical wrap-up discussing the drug use trends, adverse events and the efficacy of both oral and topical tazarotene.

Jill Lindstrom, M.D., FDA, spoke on the "Evolution of Risk Management for Systemic Retinoids." She provided an overview of the background of the retinoids currently approved for use by FDA, their historical development of risk management for systemic retinoids and in summary she states that all approved systemic retinoids are known or highly suspect potent human teratogens, risk management plans should incorporate the current best practices and current best practices for pregnancy prevention include, labeling, targeted education, reminder systems and controlled distribution.

Ann Trontell, M.D., M.P.H. FDA, discussed the "Potential Risk Management Tools for Oral Tazarotene: Context, Considerations, and Experience." She described the risk management in the context of the PDUFA3 Draft Guidance's, discussed the advantages and disadvantages of different tools, described the isotretinoin risk management for teratogenicity and placed the options proposed by the sponsor for tazarotene into context. She summarized that the systemic retinoid teratogenicity risk management plan for isotretinoin has evolved over time and the tazarotene RiskMAP has proposals for a reminder system for females of child bearing potential and a registry for physicians and pharmacists similar to that of the S.M.A.R.T. system.

The committee asked clarifying questions of the FDA presenters and then adjourned at 12:05 for lunch.

The meeting resumed at 1:00. The Open Public Hearing (OPH) had 3 speakers registered. Mr. White spoke about the National Psoriasis Foundation, the impact of psoriasis, and his experience as a person whose son has psoriasis. Ms. Janey Freeman spoke about her experience as a person with psoriasis and about her positive experience with oral tazarotene. Mr. Gorre spoke about his experience as a person with psoriasis and about his positive experience with oral tazarotene. The Chair asked for any other speakers for the OPH and seeing none the OPH was closed at 1:25.

The committee continued the discussion with both FDA and Allergan answering questions on a wide variety of topics. At 2:52 the committee took a break and returned at 3:00 to start answering the questions.

1. Based on the information from the clinical studies conducted for tazarotene capsules, is there an adequate demonstration of effectiveness for moderate to severe psoriasis?
    - **Efficacy was not shown at the end of the 12 week study**
    - **It did show that it is more effective than placebo (6 members)**
    - **The efficacy shown does not represent a significant benefit over what is currently on the market**
    - **The short half life could be a benefit with other types of psoriasis**
    - **Do not know the reliability of the scoring tool therefore the extent of efficacy is an issue**
    - **The drugs short half life is compelling for patients at risk of becoming pregnant and cannot reliably forgo pregnancy for a long post treatment as required for oral retinoid approved for psoriasis**
    - **Concern about off label use for acne given that the topical form is widely used for this indication, posters and non peer reviewed publications suggesting efficacy have been presented to dermatologists , and efficacy of Tazoral including remission rate and duration relative to isotretinoin (and hence risk/benefit ratio for a high risk drug) has not been established.**

    Is there an adequate demonstration of efficacy for “very severe” psoriasis?
    - **There was not enough power (15 patients) to show efficacy**

- **It is difficult to show progress in 12 weeks**
- **It showed that it cleared some and the patient may be happy with that but it did not meet the point required to pass**
- **There was no demonstration for efficacy for very severe psoriasis (5 members)**

2. Has the safety profile for this product been adequately assessed?
   A) Please provide discussion of the clinical and preclinical safety data, including comments on bone and liver abnormalities, hyperlipidemia, and teratogenicity.
      - **There is great concern about the pregnancy rate with the drug - there needs to be better follow-up**
      - **The study was inadequately powered to show safety and the demographics of the subjects need to be improved (4 members)**
      - **There was not enough information on the tendency to fracture with the bone information**
      - **Not overly concerned about hyperlipidemia as it can be treated but there was not enough data to adequately assess the drugs effect**
      - **The teratogenicity is a grave concern and a risk management plan must be implemented**
      - **The liver abnormalities were well explained in their presentation and are controllable**

   B) Please discuss any potential issues, regarding long term safety of oral tazarotene with repeated use.
      - **Currently there is not enough long term safety data**
      - **Need long term bone data and pregnancy data if the drug is going to be used long term**
      - **Need labeling to address lab abnormalities, liver function tests, and alkaline phosphatase and require continuous monitoring**
      - **Concern over the bone and pregnancy issues**

3. Given the safety and efficacy information, does the Committee find a favorable balance of risks and benefits which would support approval of this product?

   - **Yes - 3 Raimer, Schmidt, Wilkerson**
     - **With monitoring of Phase IV study**
   - **No - 9 Knudson, Epps, Katz, Ringel, Stern, Gardner, Levin, Honein**
     - **There is too much unknown**
     - **Not enough data to power the studies**
   - **Abstain - 4 Shapiro, Day, Furberg, Holmboe**
     - **Needs more data**
     - **information is missing**
     - **need to see an outline of a risk management plan to feel comfortable approving**
     - **need Phase IV study information**

4. Allergan has submitted a risk minimization proposal to the NDA that is similar to the isotretinoin SMART program. In addition, they have described in their package to the advisory committee a registry program that appears to be similar to the emerging isotretinoin risk minimization program. Both programs exempt males and females not of childbearing potential from many program requirements, including refill restrictions.
   A) Please comment on which teratogenic risk management program is preferred for tazarotene?
      - **Want consistent program across the board for all Retinoids / Teratogens**
      - **Include in risk management plan how drugs are used - "Use Data"**
      - **Do not use marketing data - use actual "use data"**

- **Concern over "use data" on script due to insurance issues**
- **Want a consistent program but have enough flexibility to allow sponsors to make changes**
- **Collect "use data" but be concerned over insurance companies denial of coverage**
- **Involve patients to increase participation**
- **Have some form of a feedback loop to practitioners to help change behaviors**

B) Please comment on the advantages and disadvantages of having teratogenicity program requirements applied solely for Female Child Bearing Potential.
- **With males there is exposure at conception and continued exposure during pregnancy if not followed**
- **A one size fits all Risk Management Program would need to follow everyone male & female alike**
- **There is a current concern about the male semen therefore they should be followed**
- **See comments for # 5**

C) Are the scientific and clinical uncertainties surrounding semen levels of tazarotenic acid a factor to be considered in tazarotene risk minimization?
- **It should be considered and more data gathered**
- **Comfortable with data presented**
- **Suggest condom use in labeling**

5.) How can FDA best address the potential clinical relevance of high tazarotenic acid levels in semen? Options might include:
- **Concerns could be alleviated by labeling information discussing restrictions**
- **This must be discussed in labeling**
- **Need to look at effect in subpopulations**
- **Animal studies needed to determine effect at dose target**

A) further delineation of the potential risks (via consultation with teratogenicity experts, additional preclinical studies, etc.)
- **More studies are needed (8 members)**
- **Need long term follow up for bone issues and efficacy rate**

B) informing clinicians and patients of the finding and its uncertain clinical relevance
- **Provide known information and allow the patient to make final judgment (6 members)**

C) recommending precautions (such as the use of condoms) pending characterization of the potential risk
- **Discuss issues with the patient and let them know we do not know and let them decide (5 members)**

The Committees added a part "D" to require additional studies - 9 members wanted more studies

Please comment on whether further risk assessment should be done and whether any cautionary language or recommendations should be made while additional risk assessment is pending.
- **Talk with the patients but don't scare them and let them decide**
- **We can only make recommendations on things we cannot enforce**

6.) What additional studies are needed? Are these studies needed before or after approval of the product?
- **There is a lot that is unknown and we need to know to make a decision**
- **Comprehension testing of the message before it is in full use**

- **Current data is inadequate for approval**
- **Need male reproductive studies before approval**
- **More discussion and movement on Risk Management Plan**
- **Study to demonstrate a better Risk - Benefit Ratio**
- **Require mandatory Adverse Event reporting**
- **More data on fracture and endocrine issues**
- **More animal (rabbit and mice) tests for low teratogenicity dose**

General Comments from the committee:

- **Should have comparison of Accutane and Trazodone for acne indication and publication of the results to show if it works thus limiting the off label use of the drug since it has been publicized as working at a professional meeting**
- **Concern that the drug is not being approved due to potential off label use**
- **FDA needs to move forward on the Risk Management Plan for Retinoids - do what ever it takes to solve outstanding problems.**
- **Given the teratogenic risk of retinoids, one key element of a risk benefit program is being sure that, that among retinoids with likely to be equivalent teratogenic risk, the most effective retinoid should used for a given indication. This makes the issue of off label use particularly important for indications which include substantial numbers of patients of child bearing potential.**