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Connecting Science, Skin and Lives™

March 24, 2006

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Dear Sir or Madam:

CITIZEN PETITION

Connetics Corporation (Connetics) submits this petition under sections 505(b) and 505(j) of the Federal Food, Drug and Cosmetic Act (FDCA) (21 U.S.C. §§ 355(b) and (j)) and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs withhold approval of any abbreviated new drug application (ANDA) for a generic version of acitretin capsules (Soriatane® (acitretin) Capsules, marketed by Connetics) until the conditions set forth in this petition are satisfied. Those conditions include:

- Establishing that a generic entrant is the "same" as Soriatane with regard to its (1) degradant profile; (2) polymorph composition (Polymorph A); and (3) manufacturing to a residual solvent specification that is no greater than that of Soriatane to control for conversion of acitretin to the teratogen, etretinate;

- Bioequivalence with regard to (1) pharmacokinetics for the parent compound as well as the active 13-cis isomer of acitretin; (2) bioequivalence in elderly patients; (3) the absence of additional or higher levels of metabolites; (4) appropriate qualification of any new metabolite(s) for teratogenicity and interaction with alcohol; and (5) equivalence of alcohol-induced generation of etretinate from generic acitretin to that observed for Soriatane;

- Post-implementation assessment of the effectiveness of the Soriatane RiskMAP to minimize undesired pregnancies while on therapy and during the 3-year post cessation period of vulnerability to etretinate-induced birth defects.

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ACTION REQUESTED

We request that the Agency carefully evaluate the important and serious public health implications in approving generic versions of this drug, which has been associated with serious birth defects.

Soriatane® is rated Pregnancy Category X and has been associated with serious birth defects. Thus, ensuring that an ANDA is the "same drug" is particularly critical for minimizing risks to patient safety.[1] It should not be considered the "same" until the ANDA applicant has evaluated the generic product as discussed in this petition; and it should not be considered "bioequivalent" until the generic applicant has conducted at least the bioequivalence testing that is discussed in this petition.[2] For the reasons set forth in this petition, the composition of a generic acitretin product should not be considered "safe" unless its risk minimization action plan (RiskMAP) is shown to be at least as effective as that in place for Soriatane®. Connetics requests that FDA not approve a generic acitretin product until all of the conditions cited below and detailed in this petition have been satisfactorily met.

STATEMENT OF GROUNDS

A. Background

1. Teratogenicity

Retinoids, as a class, are potent teratogens. Exposure of a fetus to retinoids at any time during pregnancy carries a high risk of serious fetal malformations. Systemic retinoids approved for use in the United States (e.g., isotretinoin, acitretin) are contraindicated in women of childbearing potential unless stringent conditions are met. They carry prominent black box warnings and are subject to extensive programs designed to minimize, if not eliminate, the chance that a woman

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[1] Section 505(j)(2)(A)(ii)(I) of the FDCA (21U.S.C. § 355(j)(2)(A)(ii)(I)) provides that, with regard to drugs containing only one active ingredient, any person filing an ANDA for the approval of a drug must show, among other things, that the drug has the "same" active ingredient as the approved reference listed drug (RLD). See also 21 C.F.R. § 314.127(a)(3)(i). The new drug must have the "same" labeling as the RLD with certain limited exceptions. 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(7). The drug must also be bioequivalent to the RLD (21 U.S.C. § 355(j)(2)A)(iv)). Among other reasons, FDA may refuse to approve an ANDA if "[i]nformation submitted in the abbreviated new drug application is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the abbreviated new drug application." 21 C.F.R. § 314.127(a)(6)(i). It is well-established that FDA has considerable discretion in determining how the bioequivalence standard is met. *Bristol-Myers Squibb Co. v. Shalala*, 923 F.Supp. 212 (D.D.C. 1996).

[2] FDA may also refuse to approve an ANDA if "[i]nformation submitted in the abbreviated new drug application or any other information available to FDA shows that: (A) The inactive ingredients of the drug product are unsafe for use...or (B) The composition of the drug product is unsafe...because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." 21 C.F.R. § 314.127(a)(8)(i). FDA will consider the inactive ingredients or composition of a drug product to be unsafe and refuse to approve an ANDA "if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy." 21 C.F.R. § 314.127(a)(8)(ii)(A).

would become pregnant while potentially harmful levels of a retinoid are in her system. As a Pregnancy Category X drug, "the risk of the use of the drug in pregnant women clearly outweighs any possible benefit." 21 CFR § 201.57(i)(e)

In 1986, the retinoid Tegison® (etretinate) was approved in the United States for the treatment of severe psoriasis. Etretinate is a potent teratogen with an extremely long elimination half-life (approximately 120 days) and is stored in adipose tissue. Etretinate has been detected in blood up to 2.9 years after therapy was discontinued. While etretinate was on the market, extensive measures were implemented by the drug sponsor to minimize the possibility that a woman might become pregnant while exposed to teratogenic levels of etretinate, a period determined to be a full three years after discontinuing therapy. Etretinate is no longer marketed in the United States.

In 1996, Soriatane® (acitretin) was approved in the United States for the treatment of severe psoriasis (reference Package Insert, attached). Acitretin is a retinoid and is also the principal metabolite of etretinate. Information submitted in the new drug application (NDA) for acitretin included data that were thought to demonstrate two potential safety advantages over etretinate: (a) acitretin has a significantly shorter half-life than etretinate (approximately two days vs. 120 days), and (b) acitretin does not accumulate in adipose tissue. *Medical Officer's Review of NDA 19-821 (original submission dated February 26, 1998, attached).* However, it was found subsequently that concurrent ingestion of acitretin and ethanol (e.g., from alcoholic beverages and potentially from over–the-counter cold medications) is associated with the formation of etretinate *in vivo*. Because etretinate, with its much longer elimination half-life, could be formed in the presence of alcohol, the current labeling for acitretin includes a black box warning that beverages or products containing ethanol must not be ingested by female patients during treatment or for two months after cessation of therapy with Soriatane®. Like the etretinate labeling, the labeling for acitretin includes a warning about pregnancy for at least three years following discontinuation of treatment. Because of the serious risk of birth defects, the labeling also limits the use of Soriatane® in women of reproductive potential to those who have severe psoriasis and are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. The drug is also contraindicated in women of childbearing potential unless two negative pregnancy tests have been obtained and the woman has selected and committed to use two effective forms of contraception for at least one month before beginning therapy, during therapy, and for three years after discontinuing therapy. The woman must sign a "Patient Agreement/Informed Consent for Female Patients" warning of the risk of fetal defects and ingestion of alcohol. All patients (male and female) are warned not to donate blood during and for at least three years following Soriatane® therapy to reduce the chance that a woman of childbearing potential might receive blood containing even a trace of acitretin. All patients must receive an FDA-approved Medication Guide highlighting these risks and warnings each time the drug is dispensed.

2. RiskMAP

Since acquiring ownership of the Soriatane® NDA, Connetics has implemented and enhanced a rigorous, active RiskMAP for this drug. The focus of this plan is to continuously educate women

and their health care providers about the serious risks associated with acitretin and to help prevent pregnancies from occurring during the use of this drug. Components of Connetics' plan include comprehensive contraception counseling and pregnancy testing, which are provided at no charge to the patient prior to initiating treatment. Connetics has also distributed various educational publications, including those that test the patient's understanding of the serious risks associated with Soriatane®, as well as letters to physicians and pharmacists, and maintains a 24-hour, toll-free information hotline for patients and healthcare providers. Connetics' sales representatives have undergone extensive training with emphasis on the indicated use of Soriatane only in severe psoriasis and in women of childbearing potential only where there are no other treatment alternatives. Connetics also actively monitors reported pregnancies and submits periodic reports to FDA describing the outcome of such occurrences, as well as the numbers and timing of pregnancies relative to Soriatane® exposure during treatment or within the following three years.

Connetics believes that its activities since acquiring the product have been instrumental in minimizing pregnancies among Soriatane patients, and has been working closely with FDA to enhance these measures. However, both FDA and Connetics understand that there is limited data available to quantify the reduction or elimination of pregnancies and to target further improvements in the plan. Accordingly, Connetics and FDA are currently in the process of designing a comprehensive pregnancy prevention program that will include an assessment of the effectiveness of Connetics' RiskMAP. With FDA's assistance, Connetics is developing an observational study that will actively enroll women of childbearing potential to assess risk comprehension and compliance with the pregnancy prevention program, including compliance with contraception and pregnancy testing. FDA has requested a report 12–18 months after the study has been initiated to assess the effectiveness of Connetics' RiskMAP. Connetics has also committed to continue reporting the outcome of all known pregnancies that have occurred in patients on Soriatane® and within the first three years after discontinuing therapy with Soriatane®.

B. The ANDA Must Be for the "Same" Drug

In the preamble to its 1992 final rule, FDA recognized that besides standard tests of identity, "in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness," such as crystalline structure. *57 Fed. Reg. 17950 (April 28, 1992).* The agency also commented on the importance of establishing specifications for impurities and residues in the ANDA product. These supplemental measures are particularly important for generic acitretin products where there are no United States compendial standards.

1. The level of degradants in the generic product must be no greater than that of Soriatane®.

The specifications for Soriatane® include maximum allowable levels for degradants of acitretin, some of which are structurally related to acitretin. It is not known whether these degradants are themselves teratogenic, or whether they might interact with ethanol to form teratogenic

substances. Therefore, an ANDA applicant must demonstrate that the degradants in their proposed product are qualified by comparison to Soriatane and that the acceptance criteria do not exceed those allowed for in Soriatane®. If the ANDA applicant cannot demonstrate the maintenance of these levels or if there are significant batch-to-batch variations in degradation product levels over the shelf life of the product, they must qualify the degradant with appropriate safety studies. *Draft Guidance for Industry, ANDAs: Impurities in Drug Products (FDA, August 2005).*

2. A generic drug manufacturer must establish an appropriate polymorph specification.

Acitretin has three polymorphs, but the Connetics' manufacturing process used for Soriatane® results in only one crystalline form of acitretin, polymorph A (as well as only one intermediate substance). All pivotal studies in the Soriatane® NDA (nonclinical and clinical safety and efficacy studies) were conducted with polymorph A. FDA has recognized that different polymorphs might have different chemical and physical properties and has discussed situations in which appropriate specifications are required. *Draft Guidance for Industry, ANDAs: Pharmaceutical Solid Polymorphism (FDA, December 2004).* It is not known whether different polymorphs of acitretin have different pharmacological and biochemical properties, such as different proportions of metabolites, any of which may react differently with alcohol and thus increase the teratogenic risk. As a result, labeling that is appropriate for polymorph A (Soriatane®) may not be appropriate for a generic drug that is a different polymorph or is a mixture of polymorphs, any of which could change the teratogenicity of the product. Therefore, dissolution characterization is not a surrogate for polymorph control in the generic acitretin product. The generic acitretin product must either be shown to contain only polymorph A using appropriate characterization methods, or demonstrate equivalent biological activity (metabolite formation, interactions with other active moieties, effect of alcohol on etretinate formation, etc.) and structural stability.

3. The levels of organic solvents in the generic drug substance must be no greater than is present in Soriatane

The *in vitro* metabolism of acitretin by human liver microsomes has been investigated. *Reference Knights, 2000 (attached).* The authors showed that when acitretin is in the presence of methanol, ethanol, propanol, butanol, or hexanol, the esters corresponding to those alcohols were formed. As discussed above, the long-lasting teratogen etretinate is formed from acitretin in the presence of ethanol. The possibility of teratogenic effects from other esterified compounds is unknown. The manufacture of any generic acitretin product must be controlled under a residual solvent specification that is no greater than that of the Soriatane® product to assure that no conversion to etretinate or other esterified compounds occurs. These compounds may have unknown, but perhaps potent teratogencity. Like etretinate, such compounds could also have a long half-life, or accumulate in adipose tissue.

C. The Generic Drug Must Be Bioequivalent to Soriatane®

While the FDA has considerable discretion in determining bioequivalence, we believe that the risk profile of this drug mandates that a generic not be deemed bioequivalent unless it meets certain pharmacokinetic standards, as described below. Failure to assure bioequivalence with regard to substrates that contribute to generating (or reducing the elimination of) etretinate, an acitretin-derived teratogen, may reduce the protection currently afforded women of child-bearing potential from the risk for incurring etretinate-related birth defects. The current level of protection derives from labeling instructions that were drafted in full consideration of Soriatane's pharmacokinetic profile.

1. Bioequivalence of acitretin and its major active metabolite, the 13-cis isomer of acitretin, at steady state concentrations, must be required.

Upon administration, acitretin undergoes a reversible biotransformation to 13-cis isomer of acitretin (Ro 13-7652). This has been established by observing Ro 13-7652 formation following administration of acitretin, and acitretin formation after administration of Ro 13-7652. *Division of Biopharmaceutics review of submission to NDA 19-821 (Jim McDowell, Ph.D.), April 5, 1990, attached.* As documented in Soriatane's package insert, the terminal elimination half-life of acitretin following multiple-dose administration was 49 hours (range 33–96 hrs), and the half-life of the 13-cis isomer of acitretin under the same conditions was 63 hours (range 28–157 hours). Steady state plasma concentrations of acitretin and the 13-cis isomer of acitretin are achieved within approximately three weeks. Due to the interconversion of acitretin and its 13-cis isomer, the elimination of *both* compounds is necessary for acitretin to be eliminated from the body. In large part because of this interconversion, the NDA sponsor assayed for the presence of both acitretin and the 13-cis isomer of acitretin throughout the development of Soriatane®. It should be noted that ethylesterification relates only to acitretin and not to 13-cis acitretin (Larsen, 2000). Since, the 13-cis isomer of acitretin contributes meaningfully to safety, particularly in the

presence of ethanol, both acitretin and the 13-cis isomer of acitretin should be assayed by any ANDA applicant.

Because acitretin and its major active metabolite, the 13-cis isomer of acitretin, have very long half-lives, the usual AUC truncation at 72 hours is inappropriate for establishing bioequivalence for this drug. Both compounds also demonstrate high intrasubject variability in clearance, which also indicates that AUC truncation is not appropriate in this case. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drugs—General Considerations (FDA, March 2003).* Connetics believes that bioequivalence to demonstrate adequate safety for this product can only be established after collecting blood samples extending out to at least five half-lives. Furthermore, an adequate washout period (at least 5 half-lives, or >10 days) between treatments in a crossover study is necessary. The pharmacokinetic parameters of acitretin and the 13-cis isomer of acitretin should both meet the current bioequivalence criteria (80–125%) in fasted and fed subjects. Both compounds contribute meaningfully to the safety and efficacy of the product because of the extensive interconversion between these two compounds and their markedly different half lives. Any generic entrant must be required to demonstrate a similar mean elimination half-life and AUC and time to steady-state for both acitretin and the 13-cis isomer of acitretin. A significant deviation from these parameters may have an effect on both efficacy and safety. For example, if generic acitretin were eliminated more slowly, it would be necessary to impose a longer abstinence from alcohol and pregnancy than for the Soriatane® product due to a greater potential teratogenicity risk. Conversely, if generic acitretin were eliminated more rapidly, efficacy may be significantly affected.

2. **Bioequivalence of other metabolites must be required.**

In addition to the major biologically active metabolite discussed above (the 13-cis isomer of acitretin), at least two other metabolites of unknown biological activity have been reported. Any generic applicant should be required to demonstrate that no other metabolite is present and that metabolites are not present at a level above that specified in the approved NDA of Soriatane® unless it can be demonstrated that such a metabolite is without appreciable biologic activity. Any metabolite of the generic acitretin product that is not quantitatively and qualitatively identical to those produced following the administration of Soriatane® should be fully characterized by the generic applicant for teratogenicity and interaction with alcohol, particularly if the metabolites are present at a level of more than 0.4%. Biological activity, particularly interaction with alcohol, of such metabolites could impart a significantly increased risk of teratogenicity that is not posed by Soriatane®. *Reference N-122774, Identification of three new human blood metabolites of Ro 10-9359, attached.*

3. **Bioequivalence of acitretin and its major active metabolite, the 13-cis isomer of acitretin, in the presence of food must be required.**

Soriatane® should be taken with food because the effect of food on the bioavailability of acitretin is pronounced. Oral administration of acitretin with food approximately doubles the rate and

extent of absorption when compared to the fasting condition. After consumption of food, the bioavailability of acitretin is dose proportional after single doses of 25 mg, 50 mg, 75 mg, and 100 mg. This proportionality does not hold when the single doses are administered under fasting conditions. *Division of Biopharmaceutic review of submission to NDA 19-821 (Jim McDowell, Ph.D.), April 5, 1990, attached.* Because the side-effect profile is proportional to the plasma concentration, a generic entrant must demonstrate that under both fed and fasting conditions, plasma concentrations are similar to the Soriatane® product. If the generic product has a longer half-life under either condition, then the period of abstinence from alcohol and pregnancy should be longer for the generic product than the Soriatane® product due to a greater potential risk of teratogenicity. If bioequivalence cannot be established under both fed and fasting conditions, particularly elimination half-life, then the generic product should not be approved. *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (FDA, December 2002).*

4. **Bioequivalence of acitretin and its major active metabolite, the 13-cis isomer of acitretin, in the presence of alcohol must be required.**

As discussed above, clinical data has shown that etretinate (a retinoid with a much longer half-life) can be formed with concurrent ingestion of acitretin and ethanol. In one study, the apparent mean terminal half-life of etretinate after 6 months of therapy was approximately 120 days (range 84–168 days). The conversion of acitretin to etretinate presents a significant safety hazard, making it critical that any generic acitretin demonstrate that its conversion to etretinate in the presence of alcohol is no greater than that for Soriatane®. If the amount of etretinate derived from acitretin in the presence of alcohol is greater for a generic than for Soriatane®, the generic product would require a warning to refrain from alcohol for a longer period of time following therapy. It is likely that prescribing physicians would only explain the precautions appropriate for Soriatane®. However a pharmacist could substitute a generic acitretin product for Soriatane®. If the precautions are inappropriate for the generic product (as they would be if the generic product or its metabolites interacted differently with alcohol), then patients and physicians would be unable to use the product safely.

5. **Bioequivalence of acitretin and its major active metabolite, the 13-cis isomer of acitretin, in elderly patients must be required.**

Acitretin is a therapy prescribed predominantly in those over the age of 50. Between March 2004 and February 2005, this age group accounted for 55.3% of total prescriptions for acitretin; of those, 17.1% were over 65. A twofold increase in acitretin concentrations at steady state was seen in elderly healthy subjects compared with young subjects. The higher plasma concentrations of acitretin observed in the elderly subjects may be due to reduced plasma clearance and volume of distribution although alterations in oral drug absorption cannot be excluded. However, the terminal elimination half-life (harmonic mean) was similar for elderly (54 hours) and young (53 hours) patients. Because the elderly are a typical population to receive acitretin, any generic entrant must demonstrate that the elimination half-life is no different in the elderly from that of Soriatane® and no more divergent from that observed in young populations.

A different elimination half-life would likely significantly alter the safety and effectiveness of the product in this vulnerable patient population.

D. FDA Should Withhold Generic Approval Until the Effectiveness of the RiskMAP for Soriatane® Has Been Determined

As discussed above, Connetics has implemented a rigorous and active RiskMAP for Soriatane® designed to effectively educate women and their health care providers about the serious risks associated with acitretin, and to minimize and prevent pregnancies from occurring during and for three years after the use of this drug. Components of this plan include pregnancy counseling and testing, patient, physician, and pharmacist education and outreach, and pregnancy monitoring and reporting. In collaboration with FDA, certain components of the RiskMAP currently are being re-evaluated for further improvement. The program, even without further change, is more rigorous than that required by the current Soriatane label.

Connetics and FDA are currently designing an observational study that will actively enroll women of childbearing potential to assess risk comprehension and compliance with the current pregnancy prevention program, including compliance with contraception and pregnancy testing. In addition, Connetics has committed to continue reporting the outcome of all known pregnancies that have occurred in patients while on Soriatane® and within the first three years after discontinuing therapy with Soriatane®. FDA asked Connetics to present the data collected during the first 12–18 months after the program is implemented. Until the effectiveness of the RiskMAP is known, it cannot be assumed that Connetics' RiskMAP is adequate to address the unique concerns of patients, pharmacists, and physicians with respect to a generic product.

The approval of a generic acitretin under the current, less stringent, Soriatane label would severely undermine Connetics' efforts to strengthen the RiskMAP. Further, the introduction of generic acitretin products—even if the current RiskMAP is required of the ANDA holder—while Connetics is attempting to enroll subjects and complete the program described above would confound the interpretation of the data from the observational study. Generic substitution at the level of the pharmacy would, at a minimum, introduce an uncontrolled variable not germane to Connetics' product, and reduce the value of the information collected in the RiskMAP assessment. Connetics will have no control over the quantity or quality of information presented to patients and healthcare professionals receiving any generic product. Moreover, because of the contraindications for use, as well as the effectiveness of the current Pregnancy Prevention Program, Connetics believes that there is only a small population of women of child bearing potential from whom meaningful RiskMAP assessment information will be obtained. If that population is further diluted by patients prescribed generic acitretin, the ability to detect small differences from these RiskMAP assessments pertaining to Soriatane® will be significantly decreased, possibly obscuring important risks to patients.

For these reasons, Connetics requests that approval of generic acitretin await the determination of whether Connetics' pregnancy RiskMAP is effective. In that way, FDA and the public can be assured that the labeling for this compound and any subsequent generic entrants provides

adequate directions for use, that all appropriate safety measures have been enacted, and that both brand and generic products have adequate and similar labeling restrictions.

CONCLUSION/SUMMARY

In conclusion, because of the potential for serious birth defects with this Pregnancy Category X rated drug, the Agency should carefully consider the public health implications associated with the approval of generic versions of Soriatane®. Specifically, the Agency should withhold approval of a generic acitretin product until (1) the generic acitretin is established to be the "same" as that of Soriatane (polymorph A and degradation products of the generic acitretin have been fully qualified), (2) bioequivalence has been established using the criteria as described in this petition, and (3) the acitretin RiskMAP has been implemented and the Agency has found it to be effective.

Soriatane carries in its label black-box warnings with regard to the need for significant reproductive precautions to minimize the risk of birth defects when Soriatane is prescribed to women of child-bearing potential. Because Soriatane is in fact a *specific* polymorph (Polymorph A) and a *single* active metabolite (13-cis isomer) of acitretin, no tests have previously been conducted regarding the role of other degradants, metabolites, polymorphs, and general pharmacokinetics to the vulnerabilities associated with generating and eliminating etretinate, an acitretin-derived teratogen. The uncertainty inherent in these untested alternatives emphasizes the need to ensure that a generic is in every way the "same" drug as Soriatane, to ensure that the safeguards put in place for Soriatane offer the same level of protection to patients prescribed or dispensed a generic acitretin.

Similarly, before access to acitretin is potentially increased by the introduction of a generic entrant, a fully implemented RiskMAP that has been tested over time and found to be an effective means of reducing risk to women of child-bearing potential is a necessary prerequisite to ensuring that the greater need to protect public health is served.

Connetics therefore requests that the Agency fully consider the conditions cited above and detailed in this petition and that the Agency ensures these conditions are satisfactorily met before approving a generic acitretin product.

ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), Connetics will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information know to the petitioner, which are unfavorable to the petitioner.

Regards,

Michael Eison, Ph.D.
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ATTACHMENTS

1. Soriatane® (acitretin) Capsule Package Insert
2. Medical Officer's Review of NDA (original submission dated February 26, 1998)
3. Knights KM, Gasser R, Klemisch W. In Vitro Metabolism of Acitretin by Human Liver Microsomes: Evidence of an Acitretinoyl-coenzyme A Thioester Conjgate in the Transesterification to Etretinate. *Biochemical Pharmacology* 2000;60:507–516
4. Division of Biopharmaceutics review of submission to NDA 19-821 (Jim McDowell, Ph.D.) April 5, 1990
5. Grønhøj Larsen F, Steinkjer B, Jakobsen P, Hjorter A, Brockhoff PB. Acitretin is converted to etretinate only during concomitant alcohol intake. *British Journal of Dermatology* 2000;143:1164–1169.
6. Vane FM, Rodriguez LC, Bugge CJL. Research Report No. N-122774, Identification of three new human blood metabolites of Ro 10-9359. Hoffman–La Roche; March 27, 1984.