

Extina Is No-Go for Seborrheic Dermatitis

BY ROBERT FINN
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Extina, a formulation of 2% ketoconazole in a proprietary foam vehicle, has been deemed nonapprovable for seborrheic dermatitis by the U.S. Food and Drug Administration.

The FDA's Nov. 23, 2004, letter concluded that Extina was not approvable because a clinical trial showed that the drug was no better than the placebo foam alone.

On the other hand, the same phase III trial did show that Extina was statistically equivalent to Nizoral (2% ketoconazole in a cream base).

"The FDA's decision is disappointing and surprising," said Thomas G. Wiggins, chief executive officer of Connetics Corp. (Palo Alto, Calif.), in a prepared statement.

"Based on discussions with the FDA regarding the requirements for the phase III trial, we believe Extina met the study end points and that the [new drug application]

was approvable. We believe that Extina demonstrated efficacy and warranted approval. However, under the circumstances, we will evaluate all options for Extina."

The company plans to discuss the nonapprovable letter with the FDA.

According to the company statement, Connetics may conduct another clinical trial, or it may choose to abandon the product in favor of concentrating on other, more promising candidates in its pipeline. ■

VERBATIM

"This 'back fat' causes obvious and unattractive bumps and ripples underneath clothing."

Dr. Naomi Lawrence, on a postmenopausal phenomenon that can be addressed with tumescent liposuction, p. 10.

conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties and subepithelial corneal lesions. Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation. **Pancreatitis:** Lipid elevations occur in 25% to 50% of patients treated with Soriatane. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported. There have been rare reports of pancreatitis during Soriatane therapy in the absence of hypertriglyceridemia. **Pseudotumor Cerebri:** Soriatane and other retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Some of these events involved concomitant use of isotretinoin and tetracyclines. However, the event seen in a single Soriatane patient was not associated with tetracycline use. Early signs and symptoms include papilledema, headache, nausea and vomiting and visual disturbances. Patients with these signs and symptoms should be examined for papilledema and, if present, should discontinue Soriatane immediately and be referred for neurological evaluation and care. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS). **PRECAUTIONS: Information for Patients:** Patients should be instructed to read the Medication Guide supplied as required by law when Soriatane is dispensed. **Females of reproductive potential: Soriatane can cause severe birth defects.** Female patients must not be pregnant when Soriatane therapy is initiated, they must not become pregnant while taking Soriatane, and for at least 3 years after stopping Soriatane (see boxed CONTRAINDICATIONS AND WARNINGS). **Females of reproductive potential should also be advised that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.** This allows for elimination of the acitretin which can be converted to etretinate in the presence of alcohol. Female patients should be advised that any method of birth control can fail, including tubal ligation, and that microdosed progesterin "mini-pill" preparations are not recommended for use with Soriatane. Female patients should sign a consent form prior to beginning Soriatane therapy (see boxed CONTRAINDICATIONS AND WARNINGS). **Nursing Mothers:** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. **All Patients: Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm have been reported.** These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms. Patients should be advised that a transient worsening of psoriasis is sometimes seen during the initial treatment period. Patients should be advised that they may have to wait 2 to 3 months before they get the full benefit of Soriatane. Decreased night vision has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see ADVERSE REACTIONS). Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period and sometimes after treatment has stopped. Patients should not donate blood during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane. Because of the relationship of Soriatane to vitamin A, patients should be advised against taking vitamin A supplements in excess of minimum recommended daily allowances to avoid possible additive toxic effects. Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical UV exposure) because the effects of UV light are enhanced by retinoids. Patients should be advised that they must not give their Soriatane capsules to any other person. **For Prescribers:** Significant lower doses of phototherapy are required when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning). **Laboratory Tests:** If significant abnormal laboratory results are obtained, either dosage reduction with careful monitoring or treatment discontinuation is recommended, depending on clinical judgment. **Blood Sugar:** Some patients receiving retinoids have experienced problems with blood sugar control. In addition, new cases of diabetes have been diagnosed during retinoid therapy, including diabetic ketoacidosis. In diabetics, blood-sugar levels should be monitored very carefully. **Lipids:** In clinical studies, the incidence of hypertriglyceridemia was 66%, hypercholesterolemia was 33% and that of decreased HDL was 40%. Pretreatment and follow-up measurements should be obtained under fasting conditions. It is recommended that these tests be performed weekly or every other week until the lipid response to Soriatane has stabilized (see WARNINGS). **Liver Function Tests:** Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. It is recommended that these tests be performed prior to initiation of Soriatane therapy, at 1- to 2-week intervals until stable and thereafter at intervals as clinically indicated (see CONTRAINDICATIONS AND WARNINGS). **Drug Interactions: Ethanol:** Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see boxed CONTRAINDICATIONS AND WARNINGS). **Glibenclamide:** In a study of 7 healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide (a sulfonylurea similar to chlorpropamide) in 3 of the 7 subjects. Repeating the study with 6 healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with Soriatane is recommended. **Hormonal Contraceptives:** It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progesterin "mini-pill" preparations. Microdosed "mini-pill" progesterin preparations are not recommended for use with Soriatane. **It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.** **Methotrexate:** An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with acitretin is also contraindicated (see CONTRAINDICATIONS). **Phenytoin:** If acitretin is given concurrently with phenytoin, the protein binding of phenytoin may be reduced. **Tetracyclines:** Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS AND WARNINGS). **Pseudotumor Cerebri, Vitamin A and oral retinoids:** Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis A. There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, or diltiazem. **Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumatin type (warfarin) revealed no interaction.** **Osteoporosis, Mutagenesis and Impairment of Fertility:** A carcinogenesis study of acitretin in Wistar rats at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80-week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m² comparison. **Mutagenesis:** Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79)HPRT assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays. **Impairment of Fertility:** In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m² comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day). No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men. No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured. **Pregnancy: Teratogenic Effects: Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).** **Nursing Mothers:** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostosis, decreases in bone mineral density, and premature epiphyseal closure have been reported in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between these effects and Soriatane has not been established. While it is not known that these occurrences are more severe or more frequent in children, there is special concern in pediatric patients because of the implications for growth potential (see WARNINGS: Hyperostosis). **Geriatric Use:** Clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A two-fold increase in acitretin plasma concentrations was seen in

healthy elderly subjects compared with young subjects, although the elimination half-life did not change. **ADVERSE REACTIONS:** During clinical trials with Soriatane, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred-sixty patients (22%) left studies prematurely, primarily because of adverse experiences involving the mucous membranes and skin. Three patients died. Two of the deaths were not drug related (pancreatic adenocarcinoma and lung cancer); the other patient died of an acute myocardial infarction, considered remotely related to drug therapy. In clinical trials, Soriatane was associated with elevations in liver function test results or triglyceride levels and hepatitis. **Postmarketing Reports: Cardiovascular:** Acute myocardial infarction, thromboembolism (see WARNINGS), stroke. **Nervous System:** Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug. **Psychiatric:** Aggressive feelings, and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane (see PRECAUTIONS). **Reproductive:** Vulvo-vaginitis due to *Candida albicans*; Skin and Appendages: Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed. Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, neuropsychiatric, and central nervous systems. Many of the clinical adverse reactions reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome. The following information lists by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis. **Adverse Events Frequently Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: CNS: 10% to 25%; Rigors: Eye Disorders: 10% to 25%; Xerophthalmia, Mucous Membranes: >75%; Chelitis; 25% to 50%; Rhinitis; 10% to 25%; Dry mouth, Epistaxis, Musculoskeletal: 10% to 25%; Arthralgia, Spinal hyperostosis (progression of existing lesions), Skin and Appendages: 50% to 75%; Alopecia, Skin peeling; 25% to 50%; Dry skin, Nail disorder, Pruritus; 10% to 25%; Erythematous rash, Hyperesthesia, Paresthesia, Paronychia, Skin atrophy, Shiny skin. **Adverse Events Less Frequently Reported During Clinical Trials (Some of Which May Bear No Relationship to Therapy) (Percent of Patients Reporting):** BODY SYSTEM: Body as a Whole: 1% to 10%; Anorexia, Edema, Fatigue, Hot flashes, Increased appetite; <1%; Alcohol intolerance, Dizziness, Fever, Influenza-like symptoms, Malaise, Myalgia, Muscle weakness, Weight increase. **Cardiovascular:** 1% to 10%; Flushing; <1%; Chest pain, Monilia, Increased bleeding time, Intermittent claudication, Peripheral ischemia. **CNS:** 1% to 10%; Headache, Pain; <1%; Abnormal gait, Migraine, Neuritis, Pseudotumor cerebri (intracranial hypertension). **Eye Disorders:** 1% to 10%; Abnormal/blurred vision, Blepharitis, Conjunctivitis/irritation, Corneal epithelial abnormality, Decreased night vision/night blindness, Eye abnormality, Eye pain, Photophobia; <1%; Abnormal lacrimation, Chalazion, Conjunctival hemorrhage, Corneal ulceration, Diplopia, Ectropion, Itchy eyes and lids, Papilledema, Recurrent sties, Subepithelial corneal lesions. **Gastrointestinal:** 1% to 10%; Abdominal pain, Diarrhea, Nausea, Tongue disorder; <1%; Constipation, Dyspepsia, Esophagitis, Gastritis, Gastroenteritis, Glossitis, Hemorrhoids, Melena, Tenesmus, Tongue ulceration. **Liver and Biliary:** <1%; Hepatic function abnormal, Hepatitis, Jaundice, Mucous Membranes: 1% to 10%; Gingival bleeding, Gingivitis, Increased saliva, Stomatitis, Thirst, Ulcerative Stomatitis; <1%; Altered saliva, Anal disorder, Gum hyperplasia, Hemorrhage, Pharyngitis, Musculoskeletal: 1% to 10%; Arthritis, Arthrosis, Back pain, Hypertonia, Myalgia, Osteodynia, Peripheral joint hyperostosis (progression of existing lesions); <1%; Bone disorder, Olecranon bursitis, Spinal hyperostosis (new lesions), Tendinitis. **Psychiatric:** 1% to 10%; Depression, Insomnia, Somnolence; <1%; Anxiety, Dysphonia, Libido decreased, Nervousness. **Reproductive:** <1%; Atrophic vaginitis, Leukorrhea. **Respiratory:** 1% to 10%; Sinusitis; <1%; Coughing, Increased sputum, Laryngitis. **Skin and Appendages:** 1% to 10%; Abnormal skin odor, Abnormal hair texture, Bullous eruption, Cold/dammy skin, Dermatitis, Increased sweating, Infection, Psoriasisiform rash, Purpura, Pyogenic granuloma, Rash, Seborrhea, Skin fissures, Skin ulceration, Sunburn; <1%; Acne, Breast pain, Cyst, Eczema, Fungal infection, Furunculosis, Hair discoloration, Herpes simplex, Hyperkeratosis, Hypertrichosis, Hypoesthesia, Impaired healing, Otitis media, Otitis externa, Photosensitivity reaction, Psoriasis aggravated, Scroderma, Skin nodule, Skin hypertrophy, Skin disorder, Skin irritation, Sweat gland disorder, Urticaria, Vernae, Special Senses/Other: 1% to 10%; Earache, Taste perversion, Tinnitus; <1%; Ceruminosis, Deafness, Taste loss. **Urinary:** <1%; Abnormal urine, Dysuria, Penis disorder. **Laboratory:** Soriatane therapy induces changes in liver function tests in a significant number of patients. Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% (see WARNINGS). Transient, usually reversible elevations of alkaline phosphatase have been observed. The following information lists the laboratory abnormalities reported during clinical trials. **Abnormal Laboratory Test Results Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: Electrolytes: 10% to 25%; Increased: Phosphorus, Potassium, Sodium; Increased and decreased: Magnesium; 1% to 10%; Decreased: Phosphorus, Potassium, Sodium; Increased and decreased: Calcium, Chloride. **Hematologic:** 25% to 50%; Increased: Reticulocytes; 10% to 25%; Decreased: Hematocrit, Hemoglobin, WBC; Increased: Haptoglobin, Neutrophils, WBC; 1% to 10%; Increased: Bands, Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes; Decreased: Haptoglobin, Lymphocytes, Neutrophils, Reticulocytes; Increased or decreased: Platelets, RBC. **Hepatic:** 25% to 50%; Increased: Cholesterol, LDH, SGOT, SGPT; Decreased: HDL cholesterol; 10% to 25%; Increased: Alkaline phosphatase, Direct bilirubin, GGT; 1% to 10%; Increased: Globulin, Total bilirubin, Total protein; Increased and decreased: Serum albumin. **Miscellaneous:** 50% to 75%; Increased: Triglycerides; 25% to 50%; Increased: CPK, Fasting blood sugar; 10% to 25%; Decreased: Fasting blood sugar, High occult blood; 1% to 10%; Increased and decreased: Iron, Renal; 10% to 25%; Increased: Uric acid; 1% to 10%; Increased: BUN, Creatinine. **Urinary:** 25% to 50%; WBC in urine; 10% to 25%; Acetoneuria, Hematuria, RBC in urine; 1% to 10%; Glycosuria, Proteinuria. **OVERDOSAGE:** In the event of acute overdose, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, i.e., headache and vertigo. The acute oral toxicity (LD₅₀) of acitretin in both mice and rats was greater than 4000 mg/kg. In one reported case of overdose, a 32-year-old male with Darier's disease took 21 x 25 mg capsules (525 mg single dose). He vomited several hours later but experienced no other ill effects. **All female patients of childbearing potential who have taken an overdose of Soriatane must:** 1) Have a pregnancy test at the time of overdose. 2) Be counseled as per the boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections regarding birth defects and contraceptive use for at least 3 years duration after the overdose. **REFERENCES:** 1. Bertis PH, et al. *Arch Dermatol Res* (1988) 280:389-393. 2. Maier H, Honigsmann H. Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 348:1107, 1996. 3. Geiger JM, Walker M. 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SORIATANE® (acitretin)

Community-Acquired MRSA Hit L.A. Children

WASHINGTON — A clonal outbreak of community-acquired methicillin-resistant *Staphylococcus aureus* in Los Angeles County led to a high rate of hospitalizations among children in 2003, Elizabeth Bancroft, M.D., reported in a poster at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Following four skin infection outbreaks due to a particular clone of MRSA (USA 300; ST:8) in 2002, the Los Angeles County Department of Health Services made community-acquired methicillin-resistant *S. aureus* (CAMRSA) infections in hospitalized children less than 18 years of age a reportable condition for 6 months during 2003. A total of 140 cases were reported between May 5 and Nov. 7, said Dr. Bancroft of the county health department.

Mean age of the children was 6.25 years (range 0-17), 51% were female, 66% were Hispanic, 16% white, 15% black, and the remainder said they were "other." Their mean length of stay was 5.13 days (range 1-30). Diagnoses included cellulitis in 44%, abscess in 36%, and a combination of the two in 11%.

In 23%, chart notes indicated a misdiagnosis of possible insect or spider bites, and 75% of the total 135 who had been treated with antibiotics were initially treated inappropriately with β -lactams, she said at the conference, sponsored by the American Society for Microbiology.

Among 82 for whom a caregiver was interviewed, 24 (29%) had a household contact with a skin infection within a month of the child's infection.

Other nosocomial risk factors were present in 29 (35%), while risk factors for community-acquired infection were present in 38 (46%), including 9 (11%) who had contact with a recently incarcerated person.

Of 83 isolates analyzed, 79 (96%) were consistent with the USA 300; ST:8 CAMRSA genotype, even though many of the children had nosocomial risk factors. During the 6 months, the 140 pediatric CAMRSA cases in Los Angeles far outnumbered other common reportable diseases, including salmonella (99) and invasive pneumococcal disease (84), she noted.

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