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NDA

019369

AP

LTR

SEP 30 1986

NDA 19-369

Linda S. Dujack, Ph.D.  
Hoffmann-La Roche, Inc.  
Nutley, New Jersey 07110

Dear Dr. Dujack:

Reference is made to your New Drug Application dated December 20, 1984, submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Tegison (etretinate) Capsules.

Reference is also made to your additional communications dated August 5, September 10 and September 25, 1986.

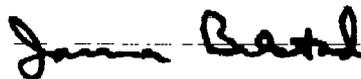
We have completed the review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on September 25, 1986. Accordingly, the application is approved, effective on the date of this letter.

Please submit the following when available:

1. Twelve copies of the final printed Patient Information Folder.
2. One market package of each size of the drug.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,



Elaine C. Esber, M.D.

Director

Office of Biologics Research and Review  
Center for Drugs and Biologics

Major human fetal abnormalities related to Tegison administration have been reported, including meningoencephalocele, meningoencephalocele, multiple synostoses, facial dysmorphism, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray.

Women of childbearing potential should not be given Tegison until pregnancy is excluded. A pregnancy test is to be performed within two weeks prior to initiating Tegison therapy. An effective form of contraception should be used for at least one month before Tegison therapy, during therapy, and following discontinuation of Tegison therapy (as noted above).

Females should be fully counseled on the serious risks to the fetus should they become pregnant while undergoing treatment or after discontinuation of therapy. If pregnancy does occur during this time, the physician and patient should discuss the desirability of continuing the pregnancy.

In addition, information about the relative frequency of congenital abnormalities among the fetuses or infants of women who have taken etretinate during the first trimester of pregnancy (either while participating in clinical trials or taking the drug where marketed in other countries) should be added to the second paragraph above. An example of how this information might be presented is as follows:

Of [number] women known to have taken one or more doses of etretinate during the first trimester of pregnancy, and for whom follow-up information was available and an abortion was not induced, [number] had spontaneous abortions and [number] delivered a term or near-term infant. The proportion of non-minor congenital abnormalities was [number] % among the aborted fetuses and [number] % among the delivered infants.

- b. The first two paragraphs of the "Pharmacokinetics" subsection of the CLINICAL PHARMACOLOGY section should be revised as follows:

The pharmacokinetic profile of etretinate is predictable and is linear following single and multiple doses. Etretinate is extensively metabolized following oral dosing, with significant first-pass metabolism to the acid form, which also has the all-trans structure and is pharmacologically active. Subsequent metabolism results in the 13-cis acid form, chain-shortened breakdown products, and conjugates that are ultimately excreted in the bile and urine.

After a six-month course of therapy with doses ranging from 25 mg once daily to 25 mg four times daily,  $C_{max}$  values ranged from 102 to 389 ng/ml and occurred at  $T_{max}$  values of 2 to 6 hours. In one study the apparent terminal half-life after six months of therapy was approximately 120 days. In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 5 to 120 ng/ml) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

- c. We do not agree with the suggestion in your letter of November 14, 1985, which would revise the INDICATIONS AND USAGE section to permit Tegison to be used as initial therapy in certain cases. The toxicity associated with this product dictates that standard therapies be tried first.
- d. In the INDICATIONS AND USAGE section:
- i. The first sentence of the first paragraph should read as follows:

Tegison is indicated for the treatment of severe recalcitrant psoriasis, including the erythrodermic and generalized pustular types.
  - ii. The last part of the last sentence of the first paragraph should read as follows:

...topical tar plus UVB light; psoralens plus UVA light; systemic corticosteroids; and methotrexate.
  - iii. The word "significant" should be deleted from the first sentence in the second paragraph.
  - iv. The word "furthermore" should be deleted from the second sentence in the second paragraph.
- e. In the WARNINGS section:
- i. The Hepatotoxicity subsection should include a statement of the number of patients who were diagnosed as having hepatitis considered possibly or probably related to etretinate therapy and the total number of patients treated. A statement should also be included about the reversibility or irreversibility of the hepatitis after etretinate was discontinued.
  - ii. The "Corneal opacities" subsection should be retitled "Ophthalmic effects" and should read as follows:

In a two-year study, male or female Sprague-Dawley rats given tretinate by dietary admixture at doses up to 3 mg/kg/day (2 times the maximum recommended human therapeutic dose) had no increase in tumor incidence.

In an 80-week study, Crl:CD-1 (ICR) BR mice were given tretinate by dietary admixture at doses of 1-5 mg/kg/day. An increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas in several different tissue sites) was noted in the high-dose male group (4-5 mg/kg/day, but not in the female group.

- iii. An additional paragraph should be added to the "Impairment of Fertility" subsection, as follows:

No adverse effects on sperm production were noted in 12 psoriatic patients given 75 mg/day of tretinate for one month and 50 mg/day for an additional two months. However, testicular atrophy was noted in subchronic and chronic rat studies and in a chronic dog study, in some cases at doses approaching those recommended for use in humans. Decreased sperm counts were reported in a 13-week dog study at doses as low as 3 mg/kg/day (approximately twice the maximum recommended human dose). Spermatogenic arrest also was reported with chronic administration of the all-trans metabolite to dogs.

- iv. The PEDIATRIC USE section should read as follows:

Pediatric Use: No studies have been conducted using Teglison in children. Ossification of the interosseous membrane of the radius and ulna has been reported in a 5-year-old child during Teglison administration. Two children showed x-ray changes suggestive of premature epiphyseal closure during treatment with another systemic retinoid (Accutane/isotretinoin). Skeletal hyperostosis has also been reported in children and adults after treatment with Accutane. It is not known if any of these effects occur more commonly in children, but concern should be greater because of the growth process. Pretreatment x-rays for bone age, followed by yearly monitoring, are advised, as are pretreatment lateral x-rays of cervical and thoracic spine with follow-up at two-year intervals. Because of the lack of data on the use of tretinate in children and the possibility of their being more sensitive to effects of the drug, this product should be used only when all alternative therapies have been exhausted.

the WARNINGS section if appropriate.

- ii. The information concerning elevations of SGOT, etc. at the end of the second paragraph of the "Laboratory" subsection should be made into a separate paragraph which reads as follows:

Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by 18%, 22%, and 16% respectively, of individuals treated with Tegison. In most of the patients, the elevations were slight to moderate and became normal either during therapy or after cessation of treatment.

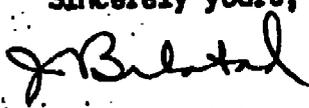
- iii. In addition to the separate paragraph discussing serum lipids and liver enzymes, the other laboratory determinations should also be grouped by using subheadings such as hematologic, blood chemistries, urinary, etc. Those abnormalities considered more likely to be related to Tegison therapy should be identified. It does not appear to be useful to list all laboratory elevations or decreases occurring at frequencies down to 1% if a relationship to drug therapy is considered to be remote. If the incidence of elevation or decrease is presented, it should be defined. Is the incidence calculated on the basis of the total number of determinations or on a per patient basis?
- iv. The increases and decreases in CO<sub>2</sub> levels noted should be clarified. Do these readings refer to plasma CO<sub>2</sub>? Was acidosis or alkalosis associated with these readings?
- v. According to the information presented, there is an increased incidence of decreased values for hemoglobin, hematocrit, and RBC, and of increased numbers of reticulocytes. In addition there appear to be increases in MCHC and MCH. Is etretinate therapy affecting red cell production or survival? How did the levels for these hematologic parameters in the etretinate-treated group compare with the placebo group in the controlled clinical trials?
- vi. The question whether Tegison therapy is associated with an adverse effect on blood coagulation factors should be specifically addressed.

materials.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

*for*  7/31/62

Elaine C. Esber, M.D.

Director

Office of Biologics Research and Review  
Center for Drugs and Biologics

HFN-220

HFN-800/ECEsber

HFN-815

HFN-815/ETabor

HFN-815/Chem/MAJarski

HFN-815/Chem/Casola

HFN-815/Pharm/JMDavitt

HFN-815/MO/WAPowell

HFN-815/DCBostwick:bam:11/5/85

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REVISED:JBILSTAD:pec:7/21/86 #0007R

Approvable

*17th*  
*7-22-86*

FPL

# TEGISON®

brand of  
etretinate/Roche

## CAPSULES

DIA  
9-30-76

ROCHE

**CONTRAINDICATION:** Tegison must not be used by females who are pregnant, who intend to become pregnant, or who are unreliable or may not use reliable contraception while undergoing treatment. The period of time during which pregnancy must be avoided after treatment has not been determined. Tegison blood levels of 0.5 to 12 ng/mL have been reported in 9 of 47 patients in the range of 2.1 to 2.9 years after treatment was concluded. The length of time necessary to wait after discontinuation of treatment to assure that no drug will be detectable in the blood has not been determined. The significance of undetectable blood levels relative to the risk of teratogenicity is unknown.

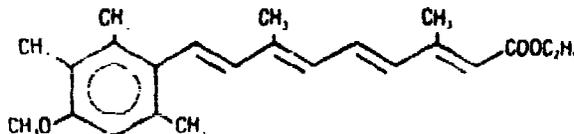
Major human fetal abnormalities related to Tegison administration have been reported, including meningomyelocele, meningoencephalocele, multiple synostoses, ... of dysmorphism, syndactyly, absence of terminal phalanx, malformations of hip, skull and forearm, low set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray.

Women of childbearing potential must not be given Tegison until pregnancy is excluded. It is strongly recommended that a pregnancy test be performed within two weeks prior to initiating Tegison therapy. Tegison therapy should start on the second or third day of the next normal menstrual period. An effective form of contraception must be used for at least one month before Tegison therapy, during therapy and following discontinuation of Tegison therapy for an indefinite period of time.

Females should be fully counseled on the serious risks to the fetus should they become pregnant while undergoing treatment or after discontinuation of therapy. If pregnancy does occur, the physician and patient should discuss the desirability of continuing the pregnancy.

**DESCRIPTION:** Tegison (brand of etretinate Roche), a retinoid, is available in 10-mg and 25-mg yellow capsules for oral administration. Each capsule also contains corn starch, lactose and talc. Gelatin capsule shells contain parabens (methyl and propyl) and potassium sorbate with the following dye systems: 10 mg—iron oxide (yellow, black and red), FD&C Blue No. 2 and titanium dioxide; 25 mg—iron oxide (yellow, black and red) and titanium dioxide.

Chemically, etretinate is ethyl (all-E)-9-(4-methoxy-2,3,5-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nontetraenoate and is related to both retinoic acid and retinol (vitamin A). It is a greenish-yellow to yellow powder with a calculated molecular weight of 354.5. The structural formula is:



**CLINICAL PHARMACOLOGY:** The mechanism of action of Tegison is unknown.

**Clinical:** Improvement in psoriatic patients occurs in association with a decrease in scale, erythema and thickness of lesions, as well as histological evidence of normalization of epidermal differentiation, decreased stratum corneum thickness and decreased inflammation in the epidermis and dermis.

**Pharmacokinetics:** The pharmacokinetic profile of etretinate is predictable and is linear following single and multiple doses. Etretinate is extensively metabolized following oral dosing, with significant first-pass metabolism to the acid form, which also has the all-trans structure and is pharmacologically active. Subsequent metabolism results in the 13-cis acid form, chain-shortened breakdown products and conjugates that are ultimately excreted in the bile and urine.

After a six-month course of therapy with doses ranging from 25 mg once daily to 25 mg four times daily, C<sub>max</sub> values ranged from 102 to 389 ng/mL and occurred at T<sub>max</sub> values of two to six hours. In one study the apparent terminal half-life after six months of therapy was approximately 120 days. In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 0.5 to 12 ng/mL) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

Etretinate is more than 90% bound to plasma proteins, predominantly lipoproteins, whereas its active metabolite, the all-trans acid form, is predominantly bound to albumin. Concentrations of etretinate in blister fluid after six weeks of dosing were approximately one-tenth of those observed in plasma. Concentrations of etretinate and its all-trans acid metabolite in epidermal specimens obtained after 1 to 36 months of therapy were a function of location: subcutis >> serum >> epidermis >> dermis. Similarly, liver concentrations of etretinate in patients receiving therapy for six months were generally higher than concurrent plasma concentrations and tended to be higher in livers with a higher degree of fatty infiltration.

In a study in normal volunteers indicated that, when compared with the fasting state, the absorption of etretinate was increased by whole milk or a high lipid diet.

**INDICATIONS AND USAGE:** Tegison is indicated for the treatment of severe psoriasis, including the erythrodermic and generalized pustular types. Because of significant adverse effects associated with its use, Tegison should be prescribed only by physicians knowledgeable in the systemic use of retinoids and reserved for patients with severe psoriasis who are unresponsive to or intolerant of standard therapies, topical tar plus UVB light, psoriasis plus UVA light, systemic corticosteroids, and methotrexate.

The use of Tegison resulted in clinical improvement in the majority of patients treated. Complete clearing of the disease was observed after four to nine months of therapy in 13% of all patients treated for severe psoriasis. This included complete clearing in 16% of patients with erythrodermic psoriasis and 37% of patients with generalized pustular psoriasis.

After discontinuation of Tegison the majority of patients experience some degree of relapse by the end of two months. After relapse, subsequent four- to nine-month courses of Tegison therapy resulted in approximately the same clinical response as experienced during the initial course of therapy.

**CONTRAINDICATIONS:** Pregnancy Category X. See boxed **CONTRAINDICATION**

**WARNINGS:**

**Pseudotumor cerebri:** Tegison and other retinoids have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Early signs and symptoms of pseudotumor cerebri include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be examined for papilloedema and, if present, they should discontinue Tegison immediately and be referred for ophthalmologic diagnosis and care.

**Hepatotoxicity:** Of the 652 patients treated in U.S. clinical trials, two had clinical or histologic hepatitis considered possibly or probably related to Tegison treatment. Liver function tests returned to normal in eight of these patients after Tegison was discontinued, one patient had histologic changes resembling chronic active hepatitis six months off therapy, and one patient had no follow-up available. There have been four reports of hepatitis-related deaths worldwide; two of these patients had received tretinoin for a month or less before presenting with hepatic symptoms. Elevations of AST (SGOT), ALT (SGPT) or LFTM have occurred in 16%, 23% and 15%, respectively, of individuals treated with Tegison. If hepatotoxicity is suspected during treatment with Tegison, the drug should be discontinued and the etiology further investigated.

**Ophthalmic effects:** Corneal erosion, abrasion, irregularity and punctate staining have occurred in patients treated with Tegison, although these effects were absent or improved after therapy was stopped in those patients who had follow-up examinations. Corneal opacities have occurred in patients receiving tretinoin; they had either completely resolved or were resolving at follow-up six to seven weeks after discontinuation of the drug. Other ophthalmic effects that have occurred in Tegison patients include decreased visual acuity and blurring of vision, night vision decrease, minimal posterior subcapsular cataract, iritis, blot retinal hemorrhage, scleritis and photophobia. Any Tegison patient experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

**Hypertostosis:** In clinical trials with Tegison, 45 patients with a mean age of 40 years have been retrospectively evaluated for evidence of hypertostosis. They had received tretinoin at a mean dose of 0.8 mg/kg for a mean duration of 33 months at the time of x-ray. Eleven patients had psoriasis, while 34 patients had a disorder of keratinization. Of these, 38 patients who continued to receive tretinoin at an average dose of 0.8 mg/kg/day for an average duration of 60 months, 32 (84%) had radiographic evidence of extraspinous tendon and ligament calcification. The most common sites of involvement were the ankles (76%), pelvis (53%) and knees (42%), spinal changes were uncommon. Involvement tended to be bilateral and multifocal. There were no bone or joint symptoms at the sites of radiographic abnormalities in 47% of the affected patients.

**Lipids:** Blood lipid determinations should be performed before Tegison is administered and then at intervals of one or two weeks until the lipid response to Tegison is established, this usually occurs within four to eight weeks.

Approximately 45% of patients receiving Tegison during clinical trials experienced an elevation of plasma triglycerides. Approximately 37% developed a decrease in high density lipoproteins and about 16% showed an increase in cholesterol levels. These effects on triglycerides, HDL and cholesterol were reversible after cessation of Tegison therapy.

Patients with an increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions.

Hypertriglyceridemia, hypercholesterolemia and lowered HDL may increase a patient's cardiovascular risk status. In addition, elevation of serum triglycerides in excess of 400 mg/dl has been associated with acute pancreatitis. Therefore, every attempt should be made to avert significant elevations of triglycerides or cholesterol or significant decreases in HDL. Some patients have been able to reverse triglyceride and cholesterol elevations or HDL decrease by reduction in weight or restriction of dietary fat and alcohol while continuing Tegison therapy.

**Cardiovascular effects:** During clinical trials of 652 patients, 21 significant cardiovascular adverse incidents were reported, all in patients who had a strong history of cardiovascular risk. These incidents were not considered related to Tegison therapy except for two cases of myocardial infarction one which was considered possibly related to Tegison therapy and one for which a relationship was not specified.

**Animal studies:** In general, the signs of tretinoin toxicity in rats, mice and dogs are dose-related with respect to incidence, onset and severity. In rodents, the most striking manifestations of this toxicity are bone fractures; no evidence of fractures was observed in a one-year dog study. Other dose-related changes in some animals treated with tretinoin in subchronic or chronic toxicity studies include alopecia, erythema, reductions in body weight and food consumption, stiffness, altered pH, hematologic changes, elevations in serum alkaline phosphatase and testicular atrophy with microscopic evidence of reduced spermatogenesis.

**PRECAUTIONS: Information for Patients:** Women of childbearing potential should be advised that they must not be pregnant when Tegison therapy is initiated, and that they should use an effective form of contraception for one month prior to Tegison therapy, while taking Tegison and after Tegison has been discontinued. Tegison has been found in the blood of some patients two to three years after the drug was discontinued. See boxed **CONTRAINDICATION**.

Because of the relationship of Tegison to vitamin A, patients should be advised against taking vitamin A supplements to avoid possible additive toxic effects.

Patients should be advised that transient exacerbation of psoriasis is commonly seen during the initial period of therapy.

Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.

**Laboratory tests:** See **WARNINGS** section. In clinical studies, the incidence of hypertriglyceridemia was one patient in two, that of hypercholesterolemia one patient in six, and that of decreased HDL one patient in three during Tegison therapy. Pretreatment and follow-up blood lipids should be obtained under fasting conditions, if alcohol has been consumed, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Tegison is established.

Elevations of AST (SGOT), ALT (SGPT) or LDH have occurred in 10%, 23% and 15%, respectively, of individuals treated with Tegison. It is recommended that these tests be performed prior to initiation of Tegison therapy, at one to two week intervals for the first one to two months of therapy and thereafter at intervals of one to three months, depending on the response to Tegison administration.

**Drug Interactions:** Little information is available on drug interactions with Tegison, however, concurrent consumption of milk increases the absorption of estradiate. See Pharmacokinetics and DOSAGE AND ADMINISTRATION sections.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

**Carcinogenesis.** In a two-year study, male or female Sprague-Dawley rats given estradiate by dietary admixture at doses up to 3 mg/kg/day (two times the maximum recommended human therapeutic dose) had no increase in tumor incidence.

In an 80-week study, Crl:CD-1 (ICR) BR mice were given estradiate by dietary admixture at doses of 1 to 5 mg/kg/day. An increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas in several different tissue sites) was noted in the high-dose male group (4 to 5 mg/kg/day) but not in the female group.

**Mutagenesis.** Estradiate was evaluated by the Ames test in a host-mediated assay, in the micronucleus test, and in a "treat and plate" test using the diploid yeast strain *S. cerevisiae* D7. Except for a weakly positive response in the Ames test using the tester strain TA 100, there was no evidence of genotoxicity. No differences in the rate of sister chromatid exchange (SCE) were noted in lymphocytes of patients before and after four weeks of treatment with therapeutic doses of estradiate.

**Impairment of Fertility.** In a study of fertility and general reproductive performance in rats, no estradiate-related effects were observed at doses up to 2.5 mg/kg/day. At a dose of 5 mg/kg/day (approximately three times the maximum recommended human therapeutic dose) the readiness of the treated animals to copulate was reduced but the pregnancy rate was unaffected. The number of viable young at birth and their postnatal weight gain and survival were adversely affected at the high dose. The pregnancy rate of the untreated first generation animals and postnatal weight gain of the untreated second generation animals were also reduced.

No adverse effects on sperm production were noted in 12 psoralea testis given 75 mg/day of estradiate for one month and 50 mg/day for an additional two months. However, testicular atrophy was noted in subchronic and chronic rat studies and in a chronic dog study, in some cases at doses approaching those recommended for use in humans. Decreased sperm counts were reported in a 13-week dog study at doses as low as 3 mg/kg/day (approximately twice the maximum recommended human dose). Spermatogenic arrest also was reported with chronic administration of the all-trans metabolite to dogs.

**Pregnancy: Category X.** See boxed CONTRAINDICATION.

The following limited preliminary data must not be read or understood to diminish the serious risk of teratogenicity set forth in the boxed pregnancy CONTRAINDICATION.

**TEGISON® (estradiol/benlate)**

Thirty women worldwide have been reported as having taken one or more doses of Tegenon during pregnancy. In 29 cases in which information was available, there were a total of ten congenital abnormalities. The occurrence of congenital abnormalities was four of 29 among delivered infants, two of two among spontaneously aborted fetuses, and four of seven among induced abortions.

A further 30 women are reported to have become pregnant within 24 months after discontinuing Tegenon therapy. Because congenital abnormalities have been reported in these pregnancies, it cannot be stated that there is a safe time to become pregnant after Tegenon therapy. In 37 cases in which information was available, there were a total of three congenital abnormalities. The occurrence of congenital abnormalities was two of 29 among delivered infants, zero of one among spontaneously aborted fetuses, and one of five among induced abortions. Two stillbirths with no apparent congenital abnormalities were attributed to other causes.

**Nonreproductive Effects:** No adverse effects on various parameters of late gestation and lactation were observed in rats at doses of estradiol up to 4 mg/kg/day (approximately three times the maximum human recommended dose). At doses of 8 mg/kg/day (approximately five times the maximum human recommended dose) of estradiol, the rate of stillbirths was increased and neonatal weight gain and survival rate were markedly reduced.

**Nursing Mothers:** Studies have shown that estradiol is secreted in the milk of lactating rats; however, it is not known whether this drug is secreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Tegenon.

**Pediatric Use:** No clinical studies have been conducted in the U.S. using Tegenon in children. Ossification of interosseous ligaments and tendons of the extremities has been reported. Two children showed x-ray changes suggestive of premature epiphyseal closure during treatment with Tegenon. Skeletal hyperostosis has also been reported after treatment with norethron. It is not known if any of these effects occur more commonly in children, but concern should be greater because of the growth process. Pretreatment x-rays for bone age including x-rays of the knees, followed by yearly monitoring, are advised. In addition, pain or limitation of motion should be evaluated with appropriate radiological examination. Because of the lack of data on the use of estradiol in children and the possibility of their being more sensitive to effects of the drug, this product should be used only when all alternative therapies have been exhausted.

**ADVERSE EVENTS; Clinical:** Hepatitis was observed in about 1.5% of patients treated with Tegenon in clinical trials. See WARNINGS section.

Tegenon has been associated with pseudotumor cerebri. See WARNINGS section.

Hypervitaminosis A produces a wide spectrum of signs and symptoms of primarily the mucocutaneous, musculoskeletal, hepatic and central nervous systems. Nearly all of the clinical adverse events reported to date with Tegenon administration resemble those of the hypervitaminosis A syndrome. Table I lists the adverse events frequently reported during clinical trials in which 652 patients were treated either for psoriasis (501 patients) or a disorder of keratinization (51 patients). Table II lists less frequently reported adverse events in these same patients.

**TABLE I  
ADVERSE EVENTS FREQUENTLY REPORTED DURING CLINICAL TRIALS  
PERCENT OF PATIENTS REPORTING (N = 652)**

BODY SYSTEM	>75%	50-75%	25-50%	10-25%
Mucocutaneous	Dry nose Chapped lips	Excessive thirst Sore mouth	Nosebleed	Cheritis Sore tongue
Dermatologic	Loss of hair Palm-sole fingertis peeling	Dry skin Itching Rash Red scaly face Skin fragility	Brusing Sunburn	Hair disorder Skin peeling
Musculoskeletal		Bone-joint pain	Muscle cramps	
Central Nervous		Fatigue	Headache	Fever
Special Senses		Irritation of eyes	Eye-eyelid abnor- malities	Abnormalities of -conjunctiva -cornea -lens -retina Conjunctivitis Decrease in visual acuity Double vision
Gastrointestinal			Abdominal pain Changes in appetite	Nausea

TABLE II  
 LESS FREQUENT ADVERSE EVENTS REPORTED DURING CLINICAL TRIALS  
 (SOME OF WHICH MAY BEAR NO RELATIONSHIP TO THERAPY)  
 PERCENT OF PATIENTS REPORTING (N = 852)

BODY SYSTEM	1-10%	<1%
Mucocutaneous	Dry eyes Mucous membrane abnormalities Dry mouth Oral bleeding/inflammation	Decreased mucus secretion Rhinorrhea
Dermatologic	Hair abnormalities Surface eruption Cold/clammy skin Dyshidrosis Paronychia Purpuric granuloma Changes in perspiration	Abnormal skin odor Granulation tissue Healing impairment Herpes simplex Herpesogen Increased pore size Sensory skin changes Skin atrophy Skin fissures Skin infection Skin nodules Skin ulceration Ulcers
Musculoskeletal	Myalgia	Stiff Hyperreflexia Hyperreflexia Hyperreflexia
Central Nervous System	Dizziness Lethargy Changes in sensation Pain Rigors	Abnormal thinking Anxiety Anxiety Depression Pseudotumor cerebri Emotional lability Faint feeling Flu-like symptoms
Special Senses	Abnormal lacrimation Abnormal vision Abnormalities of: - Extraocular musculature - Ocular tension - Pupils - Vitreous Ears/ear Otitis externa	Change in equilibrium Ear drainage Ear infection Ear itching Hearing change Light vision decrease Photophobia Visual change Vertigo
Gastrointestinal	Nausea	Constipation Diarrhea Dyspepsia Flatulence Weight loss Oral ulcers Taste perversion Tooth aches
Cardiovascular	Cardiovascular thrombotic or obstructive events Edema	Atrial fibrillation Chest pain Coagulation disorder Phlebitis Pulmonary hypertension Syncope
Respiratory	Dyspnea	Coughing Increased sputum Dysphagia Pharyngitis
Renal		Kidney stones
Urogenital		Abnormal menses Atrophic vaginitis Dysuria Purpura Urinary retention
Other	Malignant neoplasms	

**Laboratory:** Tegison therapy induces change in serum lipids in a significant number of treated patients. Approximately 45% of patients experienced elevation in serum triglycerides, 37% a decrease in high density lipoproteins and 10% an increase in cholesterol levels. Approximately 48% of patients had elevations of triglyceride above 250 mg/dL, 54% had decreases or HDL below 30 mg%, and 10% had elevations of cholesterol above 300 mg%. One case of eruptive xanthomas associated with triglyceride levels greater than 1000 mg% has been reported.

Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by 10%, 23% and 15%, respectively, of individuals treated with Tegison. In most of the patients, the elevations were slight to moderate and became normal either during therapy or after cessation of treatment. See MAJOR TOXIC SECTION.

Table III lists the laboratory abnormalities reported during clinical trials. Data for patients who received intermittent courses of therapy for periods up to five years are included. Any instance of two consecutive values outside the range of normal, or an abnormal value with no follow-up during therapy, was considered to be possibly related to Tegison.

**TABLE II:  
LABORATORY ABNORMALITIES REPORTED DURING CLINICAL TRIALS  
PERCENT OF PATIENTS REPORTING**

BODY SYSTEM	1-10%		
	25-50%	10-25%	1-10%
Hematologic	Increased -MCHC (60%) -MCH -Reticulocytes -PTT -ESR	Decreased -Hemoglobin/HCT -RBC -MCV Increased platelets Increased or decreased -WBC and components -Prothrombin time	Decreased -Platelets -MCH -MCHC -PTT Increased -Hemoglobin/HCT -RBC
Urinary		WBC in urine	Proteinuria Glycosuria Microscopic hematuria Casts in urine Acetonuria Hemoglobinuria
Hepatic	Increased Triglycerides	Increased -AST (SGOT) -ALT (SGPT) -Alkaline phosphatase -GGT -Bilirubin -Cholesterol	Increased bilirubin Increased or decreased -Total protein -Albumin
Renal			Increased -BUN -Creatinine
Electrolytes	Increased or decreased potassium	Increased or decreased -Venous CO <sub>2</sub> -Sodium -Chloride	
Miscellaneous	Increased or decreased -Calcium -Phosphorus	Increased or decreased FBS	Increased CPK

**OVERDOSE:** There has been no experience with acute overdosage in humans.

The acute oral and intraperitoneal toxicities (LD<sub>50</sub>) of estrinate capsules in mice and rats were greater than 4000 mg/kg. The acute oral toxicity (LD<sub>50</sub>) of estrinate substance in 4% solution was 2300 mg/kg in mice and 1300 mg/kg in rats.

**DOSE AND ADMINISTRATION:** There is intersubject variation in the absorption and the rate of metabolism of Tegison. Individualization of dosage is required to achieve the maximal therapeutic response with a tolerable degree of side effects. Therapy with Tegison should generally be initiated at a dosage of 0.75 to 1 mg/kg of body weight/day taken in divided doses. A maximum dose of 1.5 mg/kg/day should not be exceeded. Erythrodermic reactions may respond to lower initial doses of 0.25 mg/kg/day increased by 0.25 mg/kg/day each week until optimal initial response is attained.

Maintenance doses of 0.5 to 0.75 mg/kg/day may be initiated after initial response, generally after 8 to 16 weeks of therapy. In general, therapy should be terminated in patients whose lesions have sufficiently resolved. Relapses may be treated as outlined for initial therapy. Tegison should be administered with food.

**HOW SUPPLIED:** Brown and green capsules, 70 mg, imprinted TEGISON 70 ROCHE, Prescription Pack of 30 (NDC 0004-0177-57).

Brown and caramel capsules, 25 mg, imprinted TEGISON 25 ROCHE, Prescription Pack of 30 (NDC 0004-0178-57).

STORE AT 59° TO 86°F, 15° TO 30°C. PROTECT FROM LIGHT.

THIS PACKAGE INSERT ISSUED SEPTEMBER 1986

ROCHE LABORATORIES  
Division of Hoffmann-La Roche Inc  
Nutley, New Jersey 07110

Printed in U.S.A.

13-08-71200-0986

MEDR

Medical Officer's Review of NDA 19-369  
(Original NDA, submitted December 20, 1984)

May 7, 1985

②

Sponsor: Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110

Product: TEGISON<sup>R</sup> (etretinate) Capsules

Composition:

Purpose: For the treatment of severe recalcitrant psoriasis, especially of the erythrodermic or generalized pustular types.

Dosage: Treatment should generally be started at 0.75 to 1.0 mg/kg of body weight/day in divided doses, administered one hour before or two hours after meals. A maximum dose of 1.5 mg/kg/day should not be exceeded.

Packaging: White, opaque gelatin capsules in bottles of 100.  
Tegison 10 mg capsules are imprinted: TEGISON 10 ROCHE  
Tegison 25 mg capsules are imprinted: TEGISON 25 ROCHE

Background: Oral vitamin A has been known for many years to be effective in acne and certain keratinizing and proliferative skin diseases. Its value has been limited, however, by its side effects. Consequently, various analogs have been developed in a search for an improved therapeutic benefit/risk ratio.

Etretinate is a synthetic retinoid which showed potent antiproliferative effects in the papilloma model. Because psoriasis is a disease of marked proliferation of keratinocytes and an abnormal cellular differentiation, etretinate was used in psoriasis. The first clinical trial took place in Europe in 1975 and involved 24 patients, all of whom showed a good to excellent response, with an acceptable number and severity of side effects.

Etretinate is approved for use in 24 countries overseas.

Chemistry: Under review.

Pharmacology: Under review.

Clinical Studies

A. Pivotal Studies

Two pivotal, placebo-controlled efficacy studies were done using two protocols. Five investigators performed studies under Protocol No. 2057 (a multicenter study) and one investigator under Protocol No. 2244A.

Investigators:

Roger C. Cornell, M.D.  
Scripps Clinic Medical Group  
La Jolla, California 92037

Robert S. Gilgor, M.D.  
Chapel Hill Dermatology, P.A.  
Chapel Hill, North Carolina 27514

Gerald G. Krueger, M.D.  
University of Utah Medical Center  
Salt Lake City, Utah 84132

Jerome L. Shupack, M.D.  
New York University Medical Center  
New York, New York 10016

John J. Voorhees, M.D.  
University of Michigan Medical School  
Ann Arbor, Michigan 48109

Protocol No. 2057

Title: Evaluation of Ro 10-9359 (etretinate) vs. Placebo in Patients with Severe Psoriasis.

Objective: To evaluate the safety and efficacy of Ro 10-9359 for the treatment of psoriasis.

Method: The study was randomized and double-blind. Patients were males and females 18 years of age and over with extensive (over 20% of body surface) or disabling psoriasis (unable to carry out daily activities in a normal manner). Exclusions included patients with impaired renal or hepatic function and patients who had received any systemic drugs for psoriasis within the past month. Females of child-bearing age were to use an effective method of contraception while on treatment and for 18 months post-treatment. (Amendment [REDACTED], specified 18 months rather than the original 3 months because of the long half-life of etretinate. Also, after April 1980, no additional females of childbearing potential were to be entered into the study). No additional therapy was to be used other than a bland emollient.

The dose of etretinate and placebo was 1.0 mg/kg/day in two divided doses. Doses could be increased at 2 week intervals to 1.5 mg/kg/day. Reductions in doses could be made at any time.

The initial comparison period of drug to placebo lasted 8 weeks. At 8 weeks, placebo patients were put on etretinate for 16 more weeks; the etretinate patients were continued on drug for another 8 weeks. At the end of the 16 week periods, patients were taken off etretinate for 8 weeks. Following the off drug period, those patients who had responded well and who the investigator thought would benefit from further therapy were put on chronic therapy.

Females had a pregnancy test before starting the study. The following were done before and within one month after starting the drug:

- 1) History and physical
- 2) CBC, including reticulocytes
- 3) Urinalysis
- 4) Fasting blood sugar
- 5) BUN
- 6) Serum albumin and total protein
- 7) Serum bilirubin
- 8) SGOT, SGPT, and alk. phosphatase
- 9) Eye examination

At weeks 1, 2, 4, 8, 12 and 16 during administration of the drug and at weeks 20 and 24 while off drug, the above tests 2) through 8) were done. Follow-up eye exams were made at week 16. Patients who changed from placebo to etretinate were given tests 2) through 8) according to the same schedule. Patients who entered the chronic phase were given the same laboratory studies at least every 3 months and had eye exams yearly.

Scoring: Scale, erythema and thickness of lesions on the right and left, upper and lower body quadrants were rated (0 = absent, 1 = minimal, 2 = moderate, 3 = severe, 4 = worst possible). Length and width of the lesions were measured to the nearest centimeter. These assessments were made at baseline and at weeks 1, 2, 4 and 8 during the double-blind phase, at weeks 1, 2, 4, 8, 12 and 16 during the initial course of treatment, and at 1 and 2 months after etretinate was discontinued.

Global evaluations were made by investigators and patients according to the same time schedule (-2 = definitely worse, -1 = possibly worse, 0 = no change, 1 = minimal improvement, 2 = marked improvement, 3 = almost clear, 4 = totally clear).

For patients on chronic therapy, evaluations were made before starting and approximately every 3 months. The extent of disease was estimated as percentage of body surface involved, and scale, erythema and thickness of lesions were rated (1 = absent, 2 = trace, 3 = mild, 4 = mild to moderate, 5 = moderate, 6 = moderate to severe, 7 = severe).

**Results:** The most significant scoring methods are the investigators' global evaluations at the end of the 8 week double-blind phase of the study, and the reductions in the mean scale, erythema and lesion thickness parameters at 8 weeks.

Roger C. Cornell, M.D.

Global Evaluation at 8 Weeks

	<u>Etretinate</u> (n = 10*)	<u>Placebo</u> (n = 10*)
Definitely worse	0	2
Possibly worse	0	1
No change	0	6
Minimal improvement	3	1
Marked improvement	4	0
Almost clear	3	0
Clear	0	0

\*Ten patients in each treatment group.

100% of the etretinate group showed improvement or clearing, whereas only 10% of the placebo group did.

Percentage Reduction of Mean Scores\* of Disease Parameters at 8 Weeks

	<u>Etretinate</u> (n = 10)	<u>Placebo</u> (n = 10)	<u>Treatment Difference</u>
Scale	48.8%	2.7%	46.1%
Erythema	52.3%	- 0.64%	52.9%
Thickness	52.8%	- 2.6%	55.4%

\*Scoring: 0 = absent, 1 = minimal, 2 = mod., 3 = severe, 4 = worst possible.

Superiority of etretinate varies from 46.1% to 55.4%

Both the global evaluation and the disease parameter scores show marked clinical superiority of etretinate to placebo.

Robert S. Gilgor, M.D.

Global Evaluation at 8 Weeks

	<u>Etretinate</u> (n = 9)	<u>Placebo</u> (n = 9)
Definitely worse	1	2
Possibly worse	0	3
No change	1	3
Minimal improvement	0	0
Marked improvement	7	0
Almost clear	0	1
Clear	0	0

77.8% of etretinate patients had improvement or clearing, compared with 11.1% of placebo patients.

Percentage Reduction of Mean Scores of Disease Parameters at 8 Weeks

	<u>Etretinate</u> (n = 9)	<u>Placebo</u> (n = 9)	<u>Treatment Difference</u>
Scale	59.1%	13.5%	45.6%
Erythema	40.3%	17.7%	22.6%
Thickness	60.7%	15.5%	45.2%

Both the global evaluations and the disease parameter scores show significant clinical superiority of etretinate to placebo.

Merald G. Krueger, M.D.

Global Evaluation at 8 Weeks

	<u>Etretinate</u> (n = 9)	<u>Placebo</u> (n = 12)
Definitely worse	1	4
Possibly worse	0	1
No change	0	4
Minimal improvement	2	3
Marked improvement	6	0
Almost clear	0	0
Clear	0	0

88.9% of etretinate patients improved or cleared, compared with 25.0% of placebo patients.

Percentage Reduction of Mean Scores of Disease Parameters at 8 Weeks

	<u>Etretinate</u> (n = 9)	<u>Placebo</u> (n = 12)	<u>Treatment Difference</u>
Scale	41.0%	2.2%	38.8%
Erythema	21.6%	-8.4%	30.0%
Thickness	55.9%	-4.4%	60.3%

Both the global evaluations and the disease parameter scores show significant clinical superiority of etretinate to placebo.

Jerome L. Shupack, M.D.

Global Evaluation at 8 Weeks *Discontinuation of Therapy*

	<u>Etretinate</u> (n = 17)	<u>Placebo</u> (n = 18)
Definitely worse	0	6
Possibly worse	0	4
No change	0	6
Minimal improvement	1	0
Marked improvement	13	1
Almost clear	3	1
Clear	0	0

100% of etretinate group and 11.1% of the placebo group improved.

Percentage Reduction of Mean Scores of Disease  
Parameters at 8 Weeks

	<u>Etretinate</u> (n = 17)	<u>Placebo</u> (n = 6)	<u>Treatment Difference</u>
Scale	60.1%	28.5%	31.6%
Erythema	41.7%	27.3%	14.4%
Thickness	70.7%	22.2%	48.5%

The etretinate and placebo groups are probably too unevenly matched in numbers of patients for the results to have much significance. The results are, however, roughly consistent with those of the other investigators (except for erythema).

John J. Voorhees, M.D.

Global Evaluation at 8 Weeks

	<u>Etretinate</u> (n = 12)	<u>Placebo</u> (n = 12)
Definitely worse	0	4
Possibly worse	0	2
No change	0	1
Minimal improvement	3	4
Marked improvement	7	0
Almost clear	2	0
Clear	0	1

100% of the etretinate patients and 41.7% of the placebo patients improved.

Percentage Reduction of Mean Scores of Disease  
Parameters at 8 Weeks

	<u>Etretinate</u> (n = 12)	<u>Placebo</u> (n = 12)	<u>Treatment Difference</u>
Scale	58.6%	6.0%	48.6%
Erythema	53.7%	12.3%	41.4%
Thickness	79.0%	17.3%	61.7%

Both the global evaluations and the disease parameter scores showed significant clinical superiority of etretinate to placebo.

Pooled Results (Five Investigators) Protocol No. 2957

Pooling is permissible because the investigators followed the same protocol and because the numbers of patients per group and the results per investigator were in reasonably close agreement.

DA 19-369

Global Evaluation at 8 Weeks

	<u>Etretinate</u> (n = 57)	<u>Placebo</u> (n = 61)
Definitely worse	2	18
Possibly worse	0	11
No change	1	20
Minimal improvement	9	8
Marked improvement	37	1
Almost clear	8	2
Clear	0	1

	<u>Etretinate</u>	<u>Placebo</u>
Improved	94.7%	23.5%
Not improved	5.3%	80.3%
Marked impr. to clear	78.9%	6.6%

Percentage Reduction of Mean Scores of Disease

<u>Parameters at 8 Weeks</u>	<u>Etretinate</u> (n = 57)	<u>Placebo</u> (n = 61)	<u>Treatment Difference</u>
Scale	52.7%	10.6%	42.1%
Erythema	41.9%	8.5%	33.4%
Thickness	63.8%	9.6%	54.2%

Both the pooled global evaluations and the pooled disease parameter scores showed significant clinical superiority of etretinate to placebo.

Pooled Results with Generalized Erythrodermic Psoriasis and Generalized Pustular Psoriasis at 8 weeks (Protocol No. 2057)

The sponsor wishes to give as indications for Tegison, "severe recalcitrant psoriasis, especially of the erythrodermic or generalized pustular types."

Global Evaluations of Generalized Erythrodermic Psoriasis Patients at 8 Weeks

	<u>Etretinate</u> (n = 8)	<u>Placebo</u> (n = 6)
Definitely worse	0	2
Possibly worse	0	1
No change	0	2
Minimal improvement	0	1
Marked improvement	5	0
Almost clear	3	0
Clear	0	0

All of the etretinate patients improved. Only one placebo patient improved and he had only minimal improvement. Although the numbers of patients are small, the superiority of etretinate is marked. I consider the results probably clinically significant.

At 8 weeks, only 5 etretinate patients and 4 placebo patients were assessed for scale, erythema and thickness of lesions. Etretinate gave better results, but the numbers are too small to draw any valid conclusions about clinical significance.

Global Evaluations of Generalized Pustular Psoriasis Patients at 8 Weeks

	<u>Etretinate</u> (n = 5)	<u>Placebo</u> (n = 2)
Definitely worse	1	0
Possibly worse	0	1
No change	0	0
Minimal improvement	0	0
Marked improvement	4	0
Almost clear	0	0
Clear	0	1

These results are of no significance because of the small numbers. At the 8 week assessment of scale, erythema and thickness, the numbers were even smaller (etretinate = 3, placebo = 1).

Results after 16 Weeks of Therapy

After the initial 8 weeks of double-blind testing, placebo patients were put on etretinate for 16 weeks and etretinate patients were continued on etretinate for another 8 weeks. At the end of the 16 weeks, all patients were taken off etretinate for 8 weeks.

Global Evaluation of All Psoriasis Patients after 16 Weeks of Etretinate

	<u>week 16</u> (n = 95)	<u>8 weeks post-drug</u> (n = 85)
Definitely worse	2	45
Possibly worse	2	8
No change	0	10
Minimal improvement	7	5
Marked improvement	38	1
Almost clear	36	13
Clear	10	3

Of a total of 95 patients treated for 16 weeks, 95.8% of them improved. After two months without treatment, 62.4% of 85 patients had become worse.

Global Evaluation of Generalized Erythrodermic Psoriasis Patients after 16 Weeks of Etretinate

	<u>week 16</u> (n = 12)	<u>8 weeks post-drug</u> (n = 10)
Definitely worse	0	7
Possibly worse	0	1
No change	0	1
Minimal improvement	0	0
Marked improvement	6	0
Almost clear	4	1
Clear	2	0

All of the 12 erythrodermic psoriasis patients improved markedly or cleared after 16 weeks of therapy. Eight of the 10 patients evaluated after two months off treatment had become worse.

Global Evaluation of Generalized Pustular Psoriasis Patients after 16 Weeks of Etretinate

	<u>week 16</u> (n = 4)	<u>8 weeks post-drug</u> (n = 2)
Definitely worse	0	1
Possibly worse	0	1
No change	0	0
Minimal improvement	0	0
Marked improvement	1	0
Almost clear	2	0
Clear	1	0

All of the 4 generalized pustular psoriasis patients improved after 16 weeks of etretinate. Both of the patients evaluated after two months' layoff had relapsed.

Results of Chronic Therapy

Following the 8 week period during which patients received no etretinate, those patients who had responded well and who the investigators thought would benefit from further therapy were again given etretinate for periods up to 30 months. The patients returned every 3 months. Results were assessed by scoring the reductions in scale, erythema and thickness of lesions. Global evaluations were not made.

Percentage Reduction from Baseline in Mean Scores of Disease Parameters of all Severe Psoriasis Patients on Chronic Therapy (85 patients at baseline)

	<u>N</u>	<u>Scale</u>	<u>Erythema</u>	<u>Thickness</u>
3 mos	79	47.5%	40.5%	60.0%
6 mos	64	55.0	47.6	62.5
9 mos	63	45.0	40.5	55.0
12 mos	58	45.0	42.9	60.0
15 mos	47	47.5	47.6	62.5
18 mos	42	45.0	40.5	55.0
21 mos	37	45.0	45.2	55.0
24 mos	30	55.0	47.6	62.5
27 mos	19	50.0	52.4	57.5
30 mos	17	42.5	40.5	47.5
33 mos	7	52.5	50.0	55.0
36 mos	2	50.0	52.4	62.5

These results show that severe psoriasis patients continue to respond satisfactorily during etretinate therapy over a period of 30 months (the numbers of patients at 33 and 36 months are insignificant.)

Percentage Reduction from Baseline in Mean Scores of Disease Parameters of all Patients with Generalized Erythrodermic Psoriasis on Chronic Therapy (12 patients at baseline.)

	<u>N</u>	<u>Scale</u>	<u>Erythema</u>	<u>Thickness</u>
3 mos	12	65.7%	57.8%	76.3%
6 mos	11	57.1	60.0	65.8
9 mos	12	31.4	44.4	55.3
12 mos	11	34.3	42.2	65.8
15 mos	7	48.6	64.4	76.3
18 mos	7	40.0	48.9	63.2
21 mos	8	31.4	46.7	52.6
24 mos	6	45.7	42.2	63.2
27 mos	4	62.9	71.1	52.6
30 mos	3	51.4	55.6	47.4

These figures indicate that patients with generalized erythrodermic psoriasis continue to respond satisfactorily to etretinate therapy for up to one year, and perhaps longer. The numbers of patients from 15 mos. to 30 mos. are too small to have clinical significance.

Percentage Reduction from Baseline in Mean Scores of Disease Parameters of all Patients with Generalized Pustular Psoriasis on Chronic Therapy (5 patients at baseline).

	<u>N</u>	<u>Scale</u>	<u>Erythema</u>	<u>Thickness</u>
3 mos	5	58.3%	48.1%	81.8%
6 mos	4	62.5	75.9	65.9
9 mos	5	50.0	55.6	68.2
12 mos	2	58.3	63.0	65.9
15 mos	3	64.6	57.4	61.4
18 mos	2	79.2	63.0	54.5

I think the numbers of patients are too small to show clinical significance, although they do suggest a consistent continued response up to 18 months.

Protocol No. 2244A

Investigator: John J. Voorhees, M.D.  
University of Michigan Medical School  
Ann Arbor, Michigan 48109

Title: Mechanism of Action of Ro 10-9359 (etretinate) in Psoriasis.

Objective: To evaluate the efficacy and safety of etretinate compared with placebo for the treatment of severe psoriasis.

Method: The study was randomized and double-blind and was similar to Protocol No. 2057 in regard to patient population, patient exclusions and dosage.

The double-blind phase comparing etretinate with placebo lasted 8 weeks. At the end of 8 weeks, placebo patients were put on etretinate for 24 weeks, and etretinate patients were continued on drug for an additional 16 weeks, for a total of 24 weeks.

Global evaluations were to be made at 8 weeks and after 24 weeks of etretinate therapy and compared with baseline. Global evaluations were to be made again after patients were off the drug for 4 weeks and 8 weeks and compared with the evaluations at the end of therapy (24 weeks). The global rating scale was like that of Protocol No. 2057.

Also, scale, erythema and induration (1 = absent, 2 = trace, 3 = mild, 4 = mild to moderate, 5 = moderate, 6 = moderate to severe, 7 = severe) were scored at baseline; at weeks 1, 2, 4 and 8 during the double-blind phase; at weeks 1, 2, 8, 12, 16, 20 and 24 during the 24-week period on etretinate; and at 4 and 8 weeks after etretinate was discontinued.

Eye examinations were done before treatment and after 24 weeks of treatment. Patients were questioned regarding their family and personal histories of lipid metabolism abnormalities. At baseline and at each visit, patients were asked to check a list of signs and symptoms commonly associated with retinoid therapy, rating each for severity according to a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. And frequency of symptoms was rated on a scale of 1 = 4 times/year or less, 2 = once/month or less, 3 = once/week or more, and 4 = daily.

Results:

Global assessments were not made at the end of 8 weeks as specified in the protocol. The lesion parameters were scored, however.

Percentage Reduction of Mean Scores of Disease Parameters at 8 Weeks

	<u>Etretinate</u> (n = 15)	<u>Placebo</u> (n = 11)	<u>Treatment Difference</u>
Scale	40.0%	- 12.0%	52.0%
Erythema	28.2	2.8	25.4
Induration	44.7	- 6.3	51.0

These results show a significant clinical superiority of etretinate to placebo after 8 weeks of treatment.

Global Evaluations at the End of 24 Weeks of Etretinate Therapy and at 4 Weeks and 8 Weeks after Etretinate was Discontinued

	<u>week 24</u> (n = 27)	<u>4 weeks post-drug*</u> (n = 27)	<u>8 weeks post-drug*</u> (n = 24)
Definitely worse	0	10	12
Possibly worse	1	4	4
No change	0	2	2
Minimal improvement	1	4	1
Marked improvement	11	2	1
Almost clear	12	4	4
Clear	2	1	0

\*Compared with status at end of 24 weeks of therapy.

96.3% showed improvement after 24 weeks of therapy  
 52.0% showed worsening 4 weeks after drug stopped.  
 66.7% showed worsening 8 weeks after drug stopped.

Percentage Reductions in Mean Scores of Disease Parameters at the End of 24 Weeks of Etretinate Therapy and at 4 Weeks and 8 Weeks after Etretinate was Discontinued

	<u>n</u>	<u>Scale</u>	<u>Erythema</u>	<u>Induration</u>
Baseline	28			
Week 24	25	54.5%	57.9%	58.3%
4 Weeks post-drug	27	36.4	39.5	41.7
8 Weeks post-drug	25	21.2	18.4	16.7

At the end of 24 weeks of etretinate, there was over 50% reduction in the disease parameters, a clinically significant improvement.

Four weeks after etretinate was discontinued, the disease parameters had worsened by about 18%.

Eight weeks after etretinate was discontinued, the parameters had worsened by approximately 35 to 40%.

E. Supportive Studies

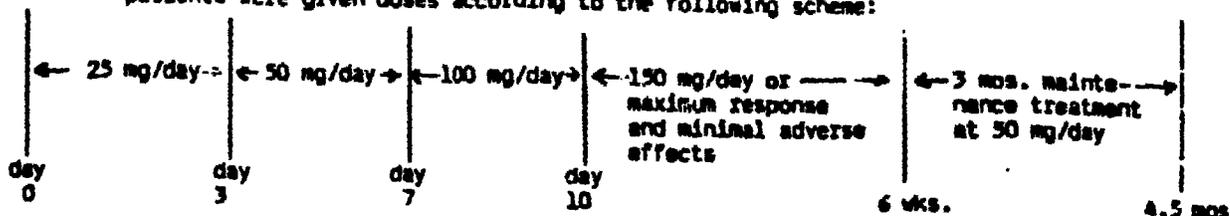
Protocol No. 898A

Investigators:

Howard Baden, M.D., Boston, ME  
 Roger C. Cornell, M.D., La Jolla, CA  
 Kenneth N. Halprin, M.D., Miami, FL  
 Leonard Harber, M.D., New York, N.Y.  
 John J. Voorhees, M.D., Ann Arbor, MI

Purpose: To evaluate the safety and efficacy of increasing doses of etretinate in severe psoriasis.

Method: This was an open, multi-center pilot study in which 20 patients were given doses according to the following scheme:



Results: Global results over-time were as follows:

<u>Time intervals in days</u>	<u>Worse</u>	<u>No Change</u>	<u>Improvement</u>
1	0	11	0
2	0	12	1
3	0	8	3
4	1	8	2
5	0	5	6
6	2	7	7
7	0	4	1
8 - 14	2	2	12
15 - 21	1	4	13
22 - 28	2	2	15
29 - 35	1	2	13
36 - 42	0	1	17
43 - 70	0	1	17
71 - 98	0	2	4
99 - 126	0	0	3
127 - 154	0	0	2

These results show that most patients improved after receiving etretinate for 6 weeks.

Protocol No. 1037A

Investigator: Gary L. Peck, M.D., NIH, Bethesda, MD.

Purpose: To evaluate the safety and efficacy of etretinate in the treatment of several disorders of keratinization, including psoriasis.

Method: This was an open, pilot study. Twenty-three patients with severe psoriasis were started on a single dose of 0.5 mg/kg. Depending on response, after 2 months the doses could be increased to 1.5 mg/kg/day maximum. Doses could be decreased at any time or dosage intervals could be changed (e.g. twice daily), depending on patients' responses and side effects. After 4 months of treatment, patients showing no response were eliminated from the study. Patients showing improvement could receive additional courses of etretinate after 2 months off the drug. After these 6-month courses, etretinate was stopped until patients began to relapse, at which time etretinate was begun again in individualized doses.

Results: Global evaluations over time were as follows:

Global Evaluations (numbers of patients in each response category)

	worse	possibly worse	no change	min. imp.	definite imp.	marked impr.	almost clear	clear
First Course	1	1	1	1	3	9	6	1
Second Course	0	0	1	1	5	6	4	0
Third Course	0	0	0	0	4	3	4	0
Fourth Course	1	0	0	0	4	4	2	0
Fifth Course	2	0	0	0	3	1	2	0
Sixth Course	0	0	0	0	2	3	0	0
Seventh Course	0	0	0	0	0	1	0	0

These results show that, by and large, most of the patients responded well to treatment.

Protocol No. 2184A

Investigators:

Eugene M. Farber, M.D., Stanford, CA  
 Evan R. Farmer, M.D., Baltimore, MD  
 Robert W. Goltz, M.D., Minneapolis, MN  
 Nicholas Lowe, M.D., Los Angeles, CA  
 Virginia C. Weiss, M.D., Chicago, IL

Purpose: To evaluate the safety and efficacy of etretinate in severe psoriasis.

Method: A multicenter, uncontrolled study of 80 psoriatics (20 patients had generalized erythrodermic psoriasis and 9 had generalized pustular psoriasis). The study was performed in two parts.

Initial Course of Treatment: Etretinate was begun at 0.75 mg/kg/day in two divided doses. The dose could be reduced to 0.5 mg/kg/day at 4, 8, or 12 weeks depending on the patient's response. The 0.75 mg/kg/day dose could then be reinitiated once at 4, 8 or 12 weeks after having started the 0.5 mg/kg/day dose. This course lasted 24 weeks maximum (unless 100% clearing occurred earlier). At the end of the initial course, global evaluations were made relative to baseline. Four weeks after stopping the drug, global evaluations were made again relative to the patient status at end of treatment.

Chronic Course of Treatment: Following a 3-month off-drug period after the initial course of treatment, those patients who had relapsed could receive additional courses at 0.5 mg/kg/day. Those patients who had severe exacerbations could receive additional treatment after waiting a minimum of 4 weeks off drug. Each chronic course was to last a maximum of 9 months. Global evaluations were made at the end of each course of chronic treatment.

JA 19-36°

Results:

Global Evaluation of All Patients at End of Initial Course

	<u>at end of initial treatment</u> (n = 86)	<u>4 wks post-treatment</u> (n = 77)
Definitely worse	3	21
Possibly worse	1	16
No change	2	20
Minimal improvement	7	6
Marked improvement	33	3
Almost clear	30	4
Clear	10	7

At the end of the initial course of treatment (max. of 24 wks.) 93% of the patients had improved; 84.9% of them were markedly improved or clear. By 4 weeks after treatment was stopped, 48% of the 77 patients had relapsed to some extent.

Global Evaluation of All Patients at End of First Chronic Course

	(n = 40)
Definitely worse	1
Possibly worse	0
No change	1
Minimal improvement	4
Marked improvement	22
Almost clear	9
Clear	3

At the end of the first chronic course of therapy, 95% of patients had improved. There were too few patients finishing the second chronic course of therapy to have any significance.

Global evaluations of 19 patients with generalized erythrodermic psoriasis at the end of the initial therapy showed that 100% of them had improved. After 4 weeks off the drug, 50% of 18 patients had worsened. At the end of the first chronic course of therapy, 100% of 10 patients had improved. There were too few after the second chronic course to be significant.

Global evaluations of 5 patients with generalized pustular psoriasis at the end of initial therapy showed all of them improved. After 4 weeks off the drug, one patient had become worse. There were too few finishing the chronic courses of therapy to have any significance.

Protocol No. 2187A

Investigator: Henry A Roenigk, Jr., M.D., Chicago, IL.

Purpose: Evaluation of the safety and efficacy of etretinate in severe psoriasis patients with increased risk of developing hepatotoxicity.

Method: This uncontrolled study was done in the same way as No. 2184A, except that liver biopsies were performed before therapy and after 24 weeks and again after the first and second chronic courses of therapy. I have not given the results of the liver biopsies in this section but include them in the adverse reactions section.

Results:Global Evaluations at End of Initial Course

	<u>at end of initial treatment</u> (n = 20)	<u>4 wks post-treatment</u> (n = 14)
Definitely worse	1	8
Possibly worse	2	0
No change	2	2
Minimal improvement	2	1
Marked improvement	4	1
Almost clear	8	1
Clear	1	1

At the end of 24 weeks, 75% of the patients were improved. Eight weeks after stopping etretinate, 57.1% of 14 patients had relapsed.

Global Evaluation at End of First Chronic Course

	(n = 10)
Definitely worse	0
Possibly worse	0
No change	0
Minimal improvement	0
Marked improvement	8
Almost clear	2
Clear	0

All of the patients improved after the first chronic course of therapy. There were too few completing the second course to have any significance.

Protocol No. 2366A

Investigator: Thomas Franz, M.D., Seattle, Wash.

Purpose: To evaluate the safety and efficacy of etretinate in severe psoriasis and to determine the pharmacokinetic profile of etretinate during and after a six-month course of treatment.

**Method:** An open study of one six-month course of etretinate was started at 25 mg/day and increased to 50 mg or 75 mg according to patient's response.

**Results:**

**Global Evaluations of All Patients**

	<u>end of treatment</u> (n = 24)	<u>4 weeks after treatment</u> (n = 23)
Definitely worse	1	11
Possibly worse	0	2
No change	0	5
Minimal improvement	3	1
Marked improvement	12	2
Almost clear	7	2
Clear	1	0

At the end of 6 months, 93.8% of the patients had improved. Four weeks after etretinate was discontinued, 56.5% of 23 patients had worsened.

**Protocol No. 2404**

**Investigators:** Thirty-three investigators took part.

**Purpose:** To enable patients with life threatening psoriasis to receive etretinate on a compassionate basis.

**Method:** An uncontrolled study in two parts.

1. An initial course of etretinate lasting 9 months or until the psoriasis cleared (if before 9 months). Dosage was individualized but usually began with 0.25 mg/kg/day and increased by 0.25 mg/kg/day each week until the best response was obtained. Maximum dose was not to exceed 1.5 mg/kg/day. At the end of 9 months, patients were put on an off-drug period of 4 weeks.
2. Chronic courses of etretinate were then given to patients who had responded to treatment and who had relapsed during the off-drug period. These patients were given additional 9 month courses of etretinate.

**Results:**

**Global Evaluation of All Patients at End of the Initial Course of Treatment**

	<u>end of initial course</u> (n = 32)	<u>4 weeks after initial course</u> (n = 14)
Definitely worse	0	11
Possibly worse	0	0
No change	0	2
Minimal improvement	1	0
Marked improvement	14	0
Almost clear	7	1
Clear	10	0

All of the 32 patients improved at the end of the initial course. Four weeks after treatment was stopped, 76.6% of 14 patients had relapsed.

At the end of the first chronic course of treatment, only 3 patients were evaluated; they all improved.

Global Evaluations of Generalized Erythrodermic Psoriasis Patients at the End of the Initial Course of Treatment

	<u>end of initial course</u> (n = 13)	<u>4 wks. after initial course</u> (n = 7)
Definitely worse	0	6
Possibly worse	0	0
No change	0	0
Minimal improvement	1	0
Marked improvement	7	0
Almost clear	3	1
Clear	2	0

All of the 13 erythrodermic psoriasis patients improved; 2 of them cleared completely. Four weeks after stopping the drug, 6 of 7 patients had worsened.

Global Evaluations of Generalized Pustular Psoriasis Patients at the End of the Initial Course of Treatment

	<u>end of initial course</u> (n = 16)	<u>4 wks. after initial course</u> (n = 4)
Definitely worse	0	2
Possibly worse	0	0
No change	0	2
Minimal improvement	0	0
Marked improvement	6	0
Almost clear	3	0
Clear	7	0

All of the 16 patients with generalized pustular psoriasis improved; 7 of them cleared completely. After 4 weeks off-drug, 2 of 4 patients had relapsed.

Protocol No. P.1

Investigator: S. Jablonska, M.D., Warsaw, Poland

The formulation used in this study was not manufactured by Hoffmann-La Roche and differed in some unspecified way from the subject formulation of this NDA. Therefore, I have not taken this study into account in evaluating results.

Adverse Reactions

The adverse effects of etretinate are mostly those of hypervitaminosis A and involve primarily the mucocutaneous, musculo-skeletal, hepatic and central nervous systems.

Summarized below are the safety results from a total of 495 patients treated with etretinate in Phase II and III studies performed in this country.

A. Laboratory Test Abnormalities

One or more lab test abnormalities occurred in 92.2% of all patients.

1. Elevation in test results:

- . Above 50 % in incidence
  - MCHC
- . 25% to 50% incidence
  - ESR
  - MCH
  - Reticulocytes
  - Partial thromboplastin time
  - Thyroid stimulating hormone
  - Triglycerides
- . 10% to 25% incidence
 

<ul style="list-style-type: none"> <li>Cholesterol</li> <li>SGOT</li> <li>SGPT</li> <li>LDH</li> <li>Monocytes</li> <li>Eosinophils</li> <li>Platelets</li> <li>Prothrombin time</li> </ul>	<ul style="list-style-type: none"> <li>Urine specific gravity</li> <li>Urine WBC</li> <li>Ig G</li> <li>Alkaline phosphatase</li> <li>GGTP</li> <li>Globulin</li> <li>Potassium</li> <li>FBS or uric acid</li> </ul>
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- . 1% to 10% incidence
 

<ul style="list-style-type: none"> <li>Hgb</li> <li>Hct</li> <li>RBC</li> <li>WBC</li> <li>Neutrophils</li> <li>bands</li> <li>Atypical lymphocytes</li> <li>Basophils</li> <li>Proteinuria</li> <li>Glycosuria</li> <li>Henaturia, microscopic</li> <li>Urinary casts</li> <li>Acetonuria</li> </ul>	<ul style="list-style-type: none"> <li>Hemoglobinuria</li> <li>Ig G</li> <li>Ig M</li> <li>Bilirubin</li> <li>Total protein</li> <li>Albumin</li> <li>BUN</li> <li>Creatinine</li> <li>Chloride</li> <li>Sodium</li> <li>CO<sub>2</sub></li> <li>Phosphorus</li> <li>Calcium or CPK</li> </ul>
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1. Decreases in test results:

- Above 50% in incidence  
HDL
- 25% to 50% incidence  
Prothrombin activity  
Phosphorus
- 10% to 25% incidence  
Hgb  
Hct  
RBC  
WBC  
MCV  
Prothrombin time  
CO<sub>2</sub>
- 1% to 10% incidence
 

Neutrophils	Ig M
Lymphocytes	Total protein
Platelets	Albumin
MCH	Chloride
MCHC	Potassium
PTT	Sodium
Urine specific gravity	FBS
Ig G	Calcium
Ig A	

B. Clinical Abnormalities

One or more abnormal signs or symptoms occurred in 62.0% of all patients. These experiences were judged to be probably or possibly related to etretinate, or the relationship was unspecified.

The following percentages of patients experienced one or more of the listed signs or symptoms:

- Over 75%
 

Peeling of palms, soles, fingertips
Chapped lips
Dry nose
Hair loss
- 50% to 75%
 

Dry skin	Pain in bones or joints
Irritation of eyes	Fatigue
Itching	Rash
Skin fragility	Red scaly face
Excessive thirst	Sore mouth

- 25% to 50%
  - Insomnia
  - Bruising
  - Nosebleed
  - Headache
  - Muscle cramps
- 10% to 25%
  - Nausea
  - Sore tongue
  - Fever
  - Diplopia
  - Nail disorder
  - Skin peeling
  - Cheilitis
  - Alopecia
- Less than 1% (relationship to treatment uncertain)
  - Acne
  - Amnesia
  - Anxiety
  - Chest pain
  - Coagulation disorder
  - Constipation
  - Coughing
  - Diarrhea
  - Dysphonia
  - Dysuria
  - Emotional lability
  - Flatulence
  - Flushes
  - Hemorrhage
  - Hair discoloration
  - Hearing impairment
  - Herpes simplex
  - Hyperesthesia
  - Hyperkinesia
  - Hypertonia
  - Postural hypotension
  - Increased pore size
  - Skin infection
  - Melena
  - Neuralgia
  - Perineal pain
  - Pharyngitis
  - Phlebitis
  - Polyuria
  - Scotomata
  - Seborrhea
  - Skin atrophy
  - Skin fissures
  - Skin nodule
  - Abnormal skin odor
  - Skin ulceration
  - Increased sputum
  - Syncope
  - Taste perversion
  - Tinnitus
  - Tongue disorder
  - Tooth caries
  - Urinary retention
  - Atrophic vaginitis
  - Faint feeling
  - Depression
  - Weight loss
  - Gout
  - Weakness
  - Decreased mucus secretion
  - Sensory skin changes
  - Poor wound healing
  - Urticaria
  - Decreased perspiration
  - Granulation tissue
  - Discolored sweat
  - Hair abnormalities
  - Gynecomastia
  - Atrial fibrillation
  - Oral ulcers
  - Enesis
  - Ocular pressure
  - Ear infection
  - Hearing change
  - Ear drainage
  - Colitis
  - Night vision decreases
  - Change in equilibrium

2. Special Topics

1. Ophthalmologic abnormalities  
Of the 495 treated patients, 283 had one or more eye examinations. Of the 283 examined, abnormal or suspect findings were noted in 147 (51.9%).

Patients with a "suspect finding" (out of 147 patients)

<u>Eye segment</u>	<u>Nb. patients</u>
Lid	67
Conjunctiva	37
Cornea	28
Lens	30
Retina	34
Other	52
Visual acuity	15
Lacrimation	6
Tension	5
Vitreous	3
Extraocular musculature	3
Pupil	2
Iris	1
Diplopia	1
Light sensitivity	1
Poor night vision	2
Shallow chamber	1
Scotoma	1

Two patients were removed from the study because of eye findings; one developed bilateral iritis and the other bilateral macular cysts.

All of the ophthalmology findings and records were submitted for review and evaluation to Paul R. Lichter, M.D., Professor and Chairman of the Ophthalmology Dept. of the University of Michigan. He judged three side effects to be definite results of etretinate treatment: loss of eyelash and eyebrow hair (15 patients), hyperemia of lids and conjunctivae (38 patients), and feelings of dryness of the eyes (17 patients). Less frequent side effects which Dr. Lichter considered important but could not definitely conclude were caused by etretinate, were: intermittent blurring of vision, minimal posterior subcapsular cataract (3 patients), iritis (2 patients), peripheral field decrease (2 patients), photophobia (1 patient), and blot retinal hemorrhages (2 patients). There were several reports of Lichter felt were unrelated to therapy.

## 2. Teratogenicity

### (a) United States

Six patients had a total of 9 pregnancies.

Six pregnancies occurred in patients who received the drug during the first trimester in doses from 0.25 to 1.25 mg/kg/day. The duration of treatment after conception was from 3 weeks to 3 months.

Three patients had therapeutic abortions and the fetuses were apparently normal.

Two patients had spontaneous miscarriages at about 5 months. One fetus had meningomyelocele. One had a metatarsus deformity of the left foot and left parieto-temporal ecchymoses. One was born normal at full term.

Three patients became pregnant 7 to 15 months after etretinate was discontinued. All three infants were reportedly normal.

### (b) Foreign

Twenty-eight pregnancies were reported during studies overseas. Among these, there were 18 live births, 2 stillbirths (one full term, one at 31 weeks), 4 therapeutic abortions, 2 spontaneous abortions, 2 malformed fetuses (no details).

Sixteen of the 28 pregnant patients received etretinate at doses of 10 to 75 mg/day for 3 to 5 months after conception. The outcomes of these pregnancies were as follows:

- 9 normal infants (1 had hemorrhagic syndrome of the neonate and 1 had ichthyosis, but no malformations).
- 3 malformed infants.
- 2 fetuses with malformations of the bones (no details).
- 1 fetus had cranial abnormalities (therapeutic abortion).
- 1 fetus had a cyst of the dura.

Nine of the 28 patients became pregnant within one year after etretinate was discontinued. Their results were as follows:

- 6 normal infants (1 had hemangiomas, however)
- 1 fetus aborted spontaneously (no report on tissue)
- 2 stillbirths (1 attributed to coiling of the umbilical cord, and 1 to impairment of circulation in the umbilical artery).

In addition to the above-described 25 pregnancies, there were 2 therapeutic abortions and 1 spontaneous abortion (no details).

### 3. Cardiovascular Reactions

There were 2 cardiovascular reactions reported whose relationship to etretinate was not specified (myocardial infarction and pulmonary embolism).

There were 7 reactions reported as possibly or probably drug related: cerebral vascular accident (remotely possible), myocardial infarction (1 case), atrial fibrillation (1 case), fragile veins (1 case), vascular flush (1 case), edema (2 cases).

There was 1 case of myocardial infarction and 1 case of pulmonary embolism (with pancreatic carcinoma leading to death) in which a drug relationship was not specified.

### 4. Hepatic Function Abnormalities

Seven patients left the study because of abnormal hepatic function. They were as follows:

		<u>Drug Relationship</u>
a.	Elevated LFT's and abnormal liver biopsy	Possible
b.	Increased SGOT, SGPT	Possible
c.	Hepatitis	Probable
d.	Acute hepatitis B	Remotely possible
e.	Fever and LFT's	Probable
f.	Liver failure, uncontrolled alcoholic, death	Not specified
g.	Elevated LFT's and chronic hepatitis	Probable
h.	Elevated LFT's	Not specified

The results of six liver function tests were as follow:

	<u>no</u>	<u>all patients</u> <u>% abnormal</u>
Alkaline phosphatase	491	17.9
SGOT	488	16.6
SGTP	420	22.9
GGTP	180	10.6
Total bilirubin	491	2.6
LDH	187	15.0

A study of the demographics of patients selected for liver function evaluation failed to reveal which patients might be at risk for developing etretinate-related liver dysfunction. The 3 cases of hepatitis were confirmed by biopsy.

The decreases in HDL and the elevation in cholesterol were reversible after etretinate was discontinued.

In Dr. Roenigk's study (2187A), patients who were at increased risk of hepatotoxicity were treated with etretinate. These included patients with increased intake of alcohol, previous use of hepatotoxins such as methotrexate, congenital liver dysfunction, liver disease as determined by more than one persistent and significant abnormality in liver function tests, or a previous abnormal liver biopsy.

Twenty-two patients had initial baseline abnormal liver biopsies. At the end of the initial course of treatment (24 weeks), 3 patients showed a worsening of their hepatic tissue status as compared to baseline, no change was shown by 16 patients and improvement was shown by 2 patients. After the first chronic course of treatment (maximum of 9 months), 14 patients had liver biopsies done and after the second chronic course of treatment (maximum of 9 months), 4 patients had liver biopsies; none of these showed any worsening in the status of the hepatic tissue.

Summary of Liver Biopsy Class Changes\* from Baseline to the End of the Initial Course

Status	class change	no. of patients
		(n = 21)
Worsened	I to II	1
	III to IV	2
	I to I	8
No change	I to I	4
	II to II	4
	III to III	
Improved	II to I	1
	III to II	1

From Baseline to the End of the First Course of Chronic Therapy

Status	class change	no. of patients
		(n = 14)
Worsened	I to IV	1
	III to IV	1
No change	I to I	5
	II to II	1
	III to III	2
Improved	II to I	2
	III to I	1
	III to II	1

From Baseline to the End of the Second Course of Chronic Therapy

		(n = 4)
Worsened		0
No change	I to IV	2
Improved	II to I	2

**\*Liver Biopsy Classes:**

I = normal to mild fatty infiltration, nuclear variability, and/or portal infiltration.

II = Moderately severe fatty infiltration, nuclear variability, portal tract expansion, portal inflammation and focal necrosis.

III = mild-mod.-severe portal fibrosis with limiting plates or septa disrupted.

IV = cirrhosis.

**5. Triglycerides**The Number of Patients with Triglyceride Elevations, by Highest Administered Dose and Blood Level

Triglyceride Level (mg/100 ml)	<u>Highest Administered Dose</u> (mg/kg/day)					Total Patients
	< 0.7	0.7 to < 0.8	0.8 to < 1.0	1.0 to < 1.1	≥ 1.1	
< 250	11	35	46	43	59	194
250 to < 500	8	37	23	26	16	110
500 to < 1500	1	1	3	2	3	10
≥ 1500	0	0	0	0	1	1
<b>Total Patients</b>	<b>20</b>	<b>73</b>	<b>72</b>	<b>71</b>	<b>79</b>	<b>315</b>
<b>Percent patients with increase of ≥ 250 mg/100 ml</b>	<b>45</b>	<b>52</b>	<b>36</b>	<b>39</b>	<b>25</b>	<b>38</b>

Except for the patient with a blood level of  $> 1500$  mg/100 ml, no apparent dose-relationship to blood levels can be concluded from these findings.

A limited number of patients seen by lipid consultants were put on corrective measures (e.g., dietary restriction, reduced alcohol intake, exercise) and successfully reduced their triglyceride levels.

About 49% of all patients given etretinate developed elevated plasma triglycerides. Those at greatest risk were diabetics, obese individuals, those with a high alcohol intake and patients with a family history of these conditions.

Triglyceride levels were reversible after etretinate was discontinued.

6. Spermatogenesis

In response to a request for information concerning the effect of etretinate on male reproduction, the sponsor submitted copies of four articles published in Retinoids, C.F. Orfanos, et al (editors), Springer-Verlag (1981).

1. Happle, R. and Niedworok, A.: Cytogenetic Studies in Patients Treated with Oral Retinoid Ro 10-9359.

A cytogenetic study was done using 9 patients with psoriasis and other skin diseases and 7 control subjects. Etretinate was given in a dose of 1.0 mg/kg/day for at least 4 weeks, then 0.5 - 1.0 mg/kg/day.

Chromosome breakage in lymphocytes was scored. The results showed no chromosomal breakage.

2. Hummler, H. and Schupbach, M.E.: Studies in Reproductive Toxicology and Mutagenicity with Ro 10-9359.

Mutagenicity studies with etretinate using *Salmonella typhimurium* and mice revealed no chromosome breaking or point mutation-inducing activity.

3. Obe, G. and Tsambaos, D.: Chromosomal Analysis in Patients with Aromatic Retinoid Ro 10-9359.

A study was made of lymphocyte chromosomes of 18 psoriatic patients who received etretinate (25 - 75 mg/day) for 4 to 24 weeks. They found no increase in chromosomal aberrations or sister chromatid exchanges. They commented that their "analysis does not answer the question whether Ro 10-9359 is capable of producing point mutations in man."

4. Schill, W.B. et al: Aromatic Retinoid and 13-cis-Retinoic Acid: Spermatological Investigations.

Twelve psoriatics received 75 mg/day of etretinate for one month, then 50 mg/day for two months. Semen was analyzed before and after treatment. Results showed that the drug did not inhibit the spermatogenetic function of the testis nor cause impaired sperm motility or morphology.

The results of these studies indicate that there is probably no adverse effect of therapeutic doses of etretinate on human spermatogenesis.

Animal studies, however, do show an effect on spermatogenesis. In a 13-week oral study in dogs, there was a decrease in sperm counts in the testes and/or epididymis in both treated and control groups, but was especially pronounced in dogs receiving 30 mg/kg/day (high dose group).

In a one-year oral study in dogs, "a slight degree of local or diffuse testicular atrophy was observed in one mid-dose dog and three high-dose dogs; reduced spermiogenesis was observed in the fourth male of the high-dose group." Also, a published report states that etretinate at a dose of 25 mg/kg/day caused impairment of spermatogenesis in guinea pigs.

In a pharmacology review.

Dr. S. R. Joshi reports that the metabolite appears to have an adverse effect on spermatogenesis in dogs. The sponsor, Hoffmann-La Roche Inc., reported in a six-month interim report of a one year oral toxicity study of Ro 10-1670 in dogs that those receiving 10 mg/kg (medium dose level) showed a slight reduction in the number of spermatozoa in the epididymis. Those who received 50 mg/kg (high dose level) showed mild to moderate spermatogenic arrest and multinucleated giant cells in the testis. The sponsor commented, "How far the mild to moderate spermatogenic arrest and the presence of multinucleated giant cells are also a consequence of the deteriorated general condition or must be considered a direct effect of the retinoid under test remains to be seen." Dr. Joshi comments that "This effect was also seen in one MDM [med. dose male] (#361). In the epididymis, the number of spermatozoa in the tubular lumen of the LD and MD dogs [low-dose and med. dose] was normal. In one MD dog (#361) and both HDM [high-dose males] the number of spermatozoa was moderately reduced. Moderate numbers of giant cells and spermatocytes with pyknotic nuclei were noted in both HDM dogs."

Labeling:

In the boxed Contraindication and Precautions sections, females of childbearing potential are advised to use an effective form of contraception for one year following discontinuation of Tegison therapy. I question whether one year is long enough, in view of the findings of J. J. Di Giovanna, et al, at the National Institutes of Health (Etretinate: Persistent Serum Levels of a Potent Teratogen, J. Invest. Dermatol. 82: 434 [abstr.], 1984. They found the following: "In 47 patients who received chronic etretinate therapy we used reverse phase HPLC to measure serum etretinate concentrations (0.05 - 1.2  $\mu$ g/dl) were observed in 5 patients more than 2 years (108, 111, 131, 136 and 150 weeks) following discontinuation of therapy (i.e., up to 7 times longer than previously reported)." Detectable serum concentrations were, therefore, detectable in those patients at 2.1, 2.1, 2.5, 2.6 and 2.9 years after discontinuation of therapy. If we assume that a concentration of etretinate as small as 0.05  $\mu$ g/dl is potentially teratogenic, then contraception should be continued for 3 years after discontinuation of therapy.

I find the package insert and the patient package insert otherwise acceptable from a medical standpoint.

Comments and Evaluation

1. This submission contains substantial evidence of the effectiveness of Tegison in severe psoriasis.
2. In spite of perhaps too few erythrodermic and pustular psoriasis cases in the pivotal studies to be significant, I feel that the total numbers and the results from both the pivotal and the supportive studies do constitute substantial and sufficient evidence of effectiveness. Out of 64 patients with generalized erythrodermic psoriasis, 98.4% improved, and 16% cleared completely at the end of the initial course of therapy. Out of 38 patients with generalized pustular psoriasis, 100% of them improved and 37% of them cleared completely.
- ✓ 3. The safety of Tegison, however, is another matter, particularly its teratogenic potential which is greater than that of Accutane.

4. I question whether post-treatment contraception for one year is long enough (as explained above in the Labeling section).
5. I question whether we have enough information regarding human spermatogenesis (as explained above under Spermatogenesis).
6. The prime question with this drug, then, is whether its probable benefits to severe psoriatics outweigh its risks, if it is used as labeled.
7. On June 24, we intend to present questions regarding efficacy and safety to the Dermatology Advisory Committee.

Recommendation:

I recommend action be deferred on this NDA until after the June 24 Dermatology Advisory Committee meeting.

*Wilson A. Powell, Jr.*  
 Wilson A. Powell, Jr., M.D.



cc:  
 Orig NDA  
 HFN-815 ET 5/22/85  
 HFN-515/CSO  
 HFN-340  
 HFN-815/CCEvans  
 HFN-815/WAPowell:js/5/16/85  
 3938b  
 C. C. E.  
 5/22/85

October 28, 1985

Addendum to Medical Officer's ReviewDate Original Review: May 7, 1985Product: Tegison (etretinate) Capsules.

Background: The Dermatologic Drugs Advisory Committee met on June 24, 1985 to consider this NDA. They recommended that the drug be approved for the treatment of severe recalcitrant psoriasis, with appropriate labeling. We are in agreement with this recommendation.

Labeling Review: The sponsor proposes to market the product with a scheme similar to that used for Accutane. A patient brochure is to be made available, as well as a patient leaflet (which is the same text as the brochure with artwork deleted). The leaflets are to be attached to the stock bottle of Tegison in a special box. Stickers stating the contraindication in pregnancy will be attached to the stock bottle and to each prescription vial. This scheme is satisfactory, but the text of the patient brochure must be updated to reflect the changes in the physician labeling agreed to by the sponsor. We recommend that the draft brochure be submitted for our review prior to printing.

Roche also plans an introductory campaign which will emphasize physician education. We recommend that FDA cooperate in this effort by publishing an article concerning Tegison in the FDA Drug Bulletin as close to the approval date of the drug as possible.

Specific comments on the package insert follow:

1. The "Pharmacokinetics" subsection of the CLINICAL PHARMACOLOGY section should contain a summary of the findings of Dr. Di Giovanna, et. al., published in the Journal of Investigative Dermatology. These findings provided the basis for the revised boxed CONTRAINDICATION section of the labeling. The information should be repeated in more detail in the Pharmacokinetics section.
2. The "Corneal opacities" subsection of the WARNINGS section should be retitled "Ophthalmic effects" and should read as follows:

Corneal erosion, abrasion, irregularity and punctate staining have occurred in patients treated with Tegison, although these effects were absent or improved in those patients who had follow-up examinations. Corneal opacities, which have tended to resolve, have occurred in patients receiving another systemic retinoid (Accutane/isotretinoin). Other ophthalmic effects which have occurred in Tegison patients include decreased visual acuity and blurring of vision, minimal posterior subcapsular cataract, iritis and blot retinal hemorrhage. Any Tegison patient experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

3. In the "Hyperostosis" subsection of the WARNING section mention should be made of this effect occurring in Tegison first (rather than mentioning this effect in Accutane patients first). In addition, further detail should be given concerning the circumstances in Tegison patients (dosage, disease, length of therapy).
4. An additional subsection should be added to the WARNINGS section following the "Lipids" subsection, to be titled "Cardiovascular effects." This subsection should address the cardiovascular reactions noted during clinical trials with Tegison. While there were not many of these effects, the probable age group of patients who will receive Tegison make this advisable.
5. An additional paragraph should be added to the "Impairment of Fertility" subsection of the PRECAUTIONS section, as follows:

While there is no direct evidence of adverse effects on male fertility in Tegison patients, animal studies on the principal metabolite of Tegison suggest that the metabolite may affect spermatogenesis.

  
Wilson A. Powell, M.D.

  
David C. Bostwick

cc:  
Orig NDA  
HFN-340  
HFN-815  
HFN-815/MO/CCEvans  
HFN-815/MO/WAPowell  
HFN-815/DCBostwick:bam:11/5/85  
0421m

ET 11/26/85

(E)

CHEM

APPLICANT:

Hoffmann-La Roche Inc.  
340 Kingsland Street  
Nutley, NJ 07110

3(a)

PRODUCT NAMES:

Tegison  
Etretinate (USAN)  
Ro 10-9359

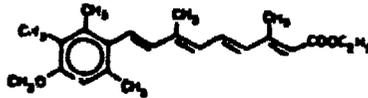
DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Hard shell gelatin capsule, oral - 10 mg. and 25 mg.

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Anti-psoriatic

STRUCTURAL FORMULA AND CHEMICAL NAMES:



C<sub>23</sub>H<sub>30</sub>O<sub>3</sub> MW: 354.49

- (1) 2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-, ethyl ester, (all-E-)
- (2) Ethyl (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate

INITIAL SUBMISSION:

Dated: December 20, 1984  
 Received: December 20, 1984  
 Assigned: January 9, 1985

METHODS VALIDATION PACKAGE:

Dated: January 31, 1985  
 Received: February 5, 1985

AMENDMENT TO METHODS VALIDATION PACKAGE:

Dated: (March 1, 1985)  
 Received: (March 5, 1985)

SUPPORTING DOCUMENTS:



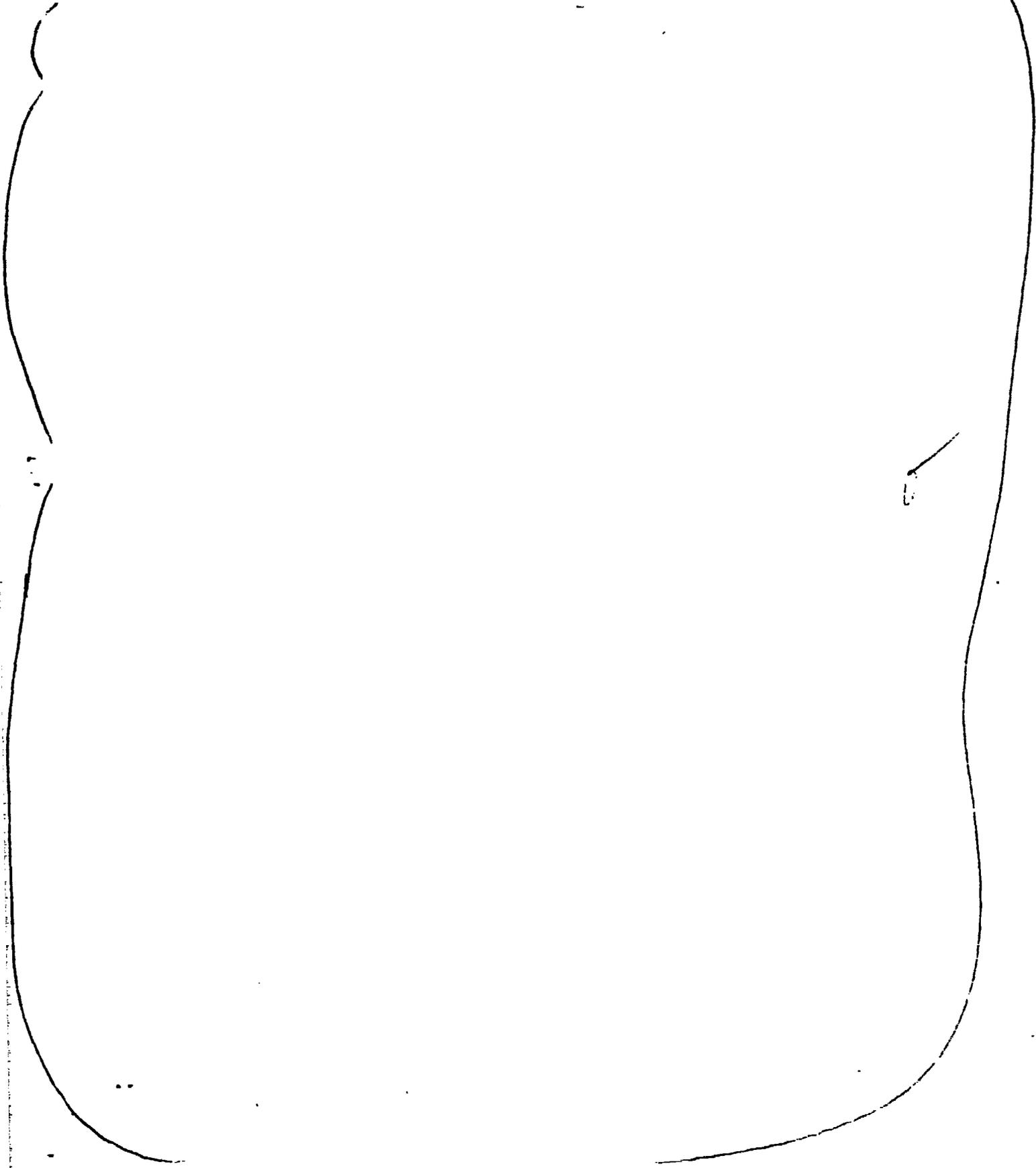
RELATED DOCUMENTS:

NDA 18-662

Roche - Accutane

COMPONENTS :

Acceptable



COMPOSITION:

Acceptable

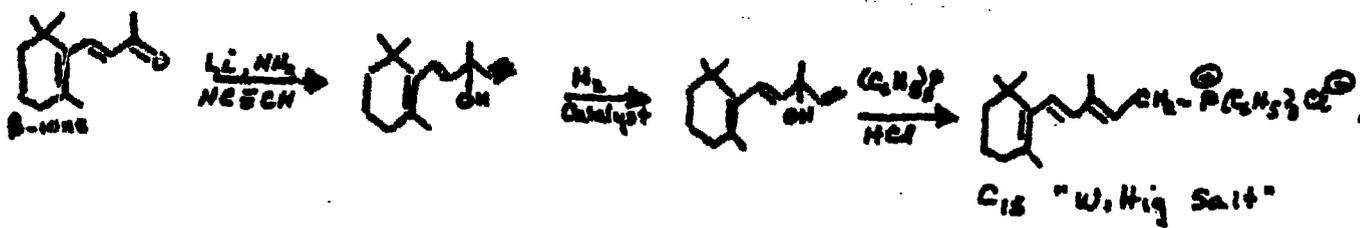
FACILITIES AND PERSONNEL:

Acceptable

SYNTHESIS:

I.

Acceptable with reservations.



RAW MATERIAL CONTROLS:

Acceptable with reservations

inate and ...e Spray-dried Powder:  
 ated below (re: V.1.118 pages 0195-0199):

13-dia % w/w	9-dia % w/w	3 13-dia % w/w	weight % w/w
n.d (A)	0.25 (c)	n.d (A)	n.d (A)
n.d (A)	0.11 (A)	n.d (A)	n.d (A)
n.d (A)	0.42 (A)	n.d (A)	n.d (A)
n.d (A)	0.38 (A)	n.d (A)	n.d (A)
n.d (A)	0.38 (A)	n.d (A)	n.d (A)
n.d (A)	0.14 (c)	n.d (A)	—
n.d (A)	0.1 (c)	n.d (A)	—
0.65 (A)	0.25 (A)	n.d (A)	n.d (A)
n.d (A)	0.22 (A)	n.d (A)	n.d (A)
n.d (A)	0.21 (A)	n.d (A)	n.d (A)
n.d (A)	0.22 (A)	n.d (A)	n.d (A)
1.98 (A)	1.44 (A)	0.11 (A)	n.d (A)
1.48 (A)	1.22 (A)	0.10 (A)	n.d (A)
1.45 (A)	0.60 (A)	0.08 (A)	n.d (A)
3.27 (A)	3.36 (A)	0.52 (A)	n.d (A)
3.31 (A)	2.39 (A)	0.52 (A)	n.d (A)
3.40 (A)	2.50 (A)	0.54 (A)	n.d (A)
1.36 (A)	0.57 (c)	0.16 (A)	—
0.98 (A)	0.39 (c)	0.14 (A)	—

CONTAINERS:

Adequate

Acceptable with reservations.

LABELING:

Draft labeling contained in the application is as follows:

1. Package insert:
  - a) DESCRIPTION Section: adequate except it does not include a listing of inactive ingredients contained in the product, as adopted by the PMA Board of Directors (12-5-84) (Note: This is voluntary)
  - b) HOW SUPPLIED Section: 10 mg. and 25 mg. imprinted, white opaque capsules in bottles of 100.
2. Package Labeling and Cautions (Rx notices are included):
  - a) Bottle label, 100's - 10 mg. and 25 mg. capsules.  
"Store at 59° - 86°F; 15° to 30°C"  
"Dispense in tight, light-resistant containers as defined by USP/NF"
  - b) Window cartons for bottles
  - c) Capsule Bulk container Label - Domestic - 10 mg. and 25 mg. capsules.  
"For manufacturing, processing or repacking."  
"Store at 59° to 86°F; 15° to 30°C."  
A space is included for lot no. and expiration date.
  - d) Capsule Bulk container Label - Export - 10 mg. and 25 mg. capsules  
"For Export Only"  
Other cautions are in accord with the Domestic labels
  - e) Label for Shipment of Bulk Etretinate  
"KG"; "Etretinate Pure"; "Made in Switzerland"; "Sealed under Nitrogen";  
"Store in a Cool Place"; "Photosensitive"

Comments: On labeling the applicant is to include:

1. An alphabetical listing of inactive ingredients contained in the product in the DESCRIPTION Section of the package insert (*VOLUNTARY*)
2. "Protect from light" on all container and carton labeling, and storage cautions should appear in the HOW SUPPLIED section of the package insert.

ESTABLISHMENT INSPECTION:

Acceptable

ENVIRONMENTAL IMPACT ANALYSIS REPORT:

SAMPLES AND RESULTS:

essentially resolved all deficiencies noted in our Draft Manufacturing  
pts, which were given to them without a formal letter from the

ponses of August 16, September 4, and October 7, 1985, the application  
n a manufacturing and controls standpoint and a 48 month expiry date  
this product.

, however, that the applicant is proposing to market product in a  
ress than was originally contained in the application. The change  
rent capsule colors and imprinting inks, there is no change in bulk  
ty data has been provided for capsules in the new trade dress and  
profiles closely match those of the originally proposed capsules.

Notes).  
validation work has not been completed. One of our laboratories was  
e the 9-cis isomer from etretinate, using the applicant's HPLC method,  
was able to do so. There were also differences in the dissolution  
wo laboratories. These are not considered trivial problems  
nvolve re-writing the methods.  
both laboratories and Roche with all the currently available  
ts and the problems are under study.

**RECOMMENDATIONS:**  
ta and information submitted to the NDA the application is approvable  
uring and controls standpoint. However, before final approval is  
nufacturing and controls portion of the application the difficulties  
our validating laboratory must be resolved.

*Mary Ann Jarski* 6/18/85

Mary Ann Jarski  
Chemist MFN-815



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ki

RCesola

MENTS AND COMPOSITION  
to Chemist's Review #1

Acceptable

**FACILITIES AND PERSONNEL:**  
Refer to Chemist's Review #1

**ANALYSIS:**  
Refer to Chemist's Review #1

Acceptable

Now Acceptable

c.

-----  
**MANUFACTURING AND PROCESSING:**  
**Refer to Chemist's Review #1.**

**Now Acceptable**

**CONTAINERS:**

**Acceptable**

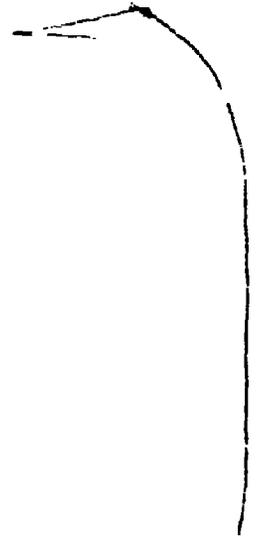
**LABORATORY CONTROLS:**

refer to Chemist's Review #1.

**Now Acceptable (pending resolution of methods validation study)**

QUALITY:  
r to Chemist's Review #1

Now Acceptable



**ESTABLISHMENT INSPECTION:**  
refer to Chemist's Review #1.

Acceptable

**ENVIRONMENTAL IMPACT:**  
refer to Chemist's Review #1

Now Acceptable

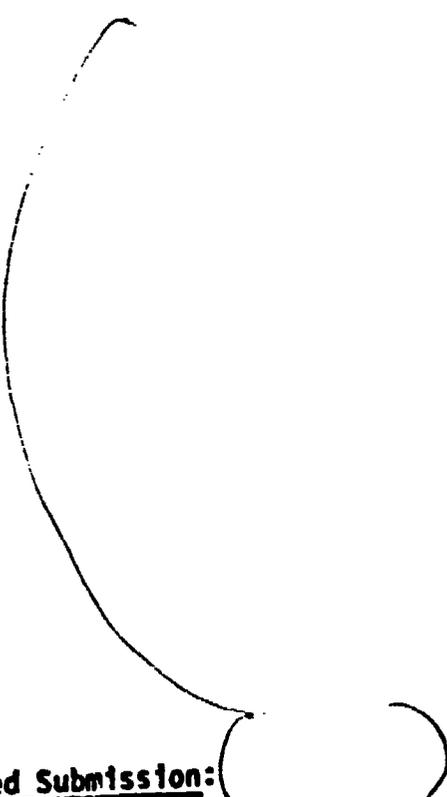
report has been amended to include environmental precautions used for dosage  
in manufacture at Nutley and advises of NJ regulations

**ANALYSES AND RESULTS:**  
refer to Chemist's Review #1.

Reports not concluded.

Both the NY Regional Laboratory and the Roche Laboratory were the assigned laboratories for validating  
methods. Both reports are attached.  
NY was able to use the Roche procedures. NY has not been able to use the HPLC  
procedure, i.e. the 9-cis isomer is not resolved from etretinate.

This problem is presently under study by WEAC, NY and Roche (refer to 10-4-85  
transmission).



Related Submission:

Clinical Indication: Psoriasis ("Reserved for patients with severe recalcitrant psoriasis who are unresponsive to or intolerant of standard therapies: topical tar and UVB light; psoralens and UVA light; or systemic corticosteroids and methotrexate.")

Dosage: Initially 0.25mpk/day increased by 0.25mpk/day each week until initial response. Maintenance dose: 0.25-0.75mpk/day. Maximum dose: 1.5mpk/day.

PRECLINICAL DATA

Note: Ro 10-9359 (Etretinate) will be abbreviated "ER".

TOXICOLOGY

Note: All studies done outside the U.S. are marked by #.

Acute Toxicity:

#1. Single Dose

Oral LD<sub>50</sub>'s for 10, 25 & 50mg capsules of spray-dried ER (suspended in gum acacia) were greater than 400, 1000 & 2000mpk, respectively.

(Please see table, next page.)

PHARM

NDA 19-369 (Original Submission, dated 12/20/84)

Date Received: 12/31/85

Date Review Completed: 5/28/85

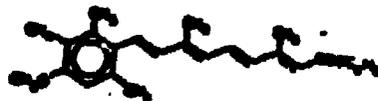
Applicant: Hoffmann-La Roche, Inc., Nutley, NJ

Drug: TEGISON<sup>®</sup> Capsules, 10mg & 25mg

Other Names: "Tigason" (Europe)  
Etretinate (USAN)  
Code Name: Ro 10-9359

Chemical Name: Ethyl (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate

Chemical Structure:



Category: Retinoid for systemic use

Formulation:



4

<u>Route</u>	<u>Days Observed</u>	<u>Dose Levels Tested (mg/kg)</u>	<u>LD<sub>50</sub> (mg/kg)</u>
<u>Mouse</u>			
Oral	1	4,000	>4000
Oral	10, 20*	2000, 4000	>2000
I.P.	1	4000	>4000
I.P.	10	1000, 2000	>1000
I.P.	20	900, 1000, 1000, 1100, 1200, 1300, 1400, 1500	1176

Rat

Oral	1, 10, 20	4000	>4000
I.P.	1, 10	4000	>4000
I.P.	20	2000, 4000	>2000

Symptoms: Mild sedation in both species and at all dose levels;  
\*Alopecia after oral treatment in the mouse 10, 20 days observation

#2. Multiple Dose

Material Tested: ER in arachis oil

		<u>LD<sub>50</sub> (mg/kg)</u>
Mice	24 hrs after 1 dose	>8000
	24 hrs after 5 doses	225
	24 hrs after 10 doses	41
	10 days after 10 doses	22
rats	24 hrs after 1 dose	>8000
	24 hrs after 5 doses	811
	24 hrs after 10 doses	64
	10 days after 10 doses	88

Dogs tolerated IV admin. of sol'n containing 0.667mg/ml ER (mixed-micelle solubilisate) in daily ascending doses of 0.5 to 4.0ml/kg without side effects.

Eight dogs (2/sex/gp) rec'd pyramiding oral doses of 10, 30, 100, 300 & 600µg ER by intubation. Additionally, 4 dogs rec'd similar doses of ER as 100mg capsules. All dogs survived. Emesis, loose feces and symptoms of hypervitaminosis A were observed.

Subacute/Chronic Toxicity#1. 4-Week Oral Toxicity in Ratsa) ER in Arachis Oil (Huntington Res. Centre, U.K.)

Sprague-Dawley (CFY) rats, 5 M/dose; dose levels of 0, 5, 10, 15 & 20mpk ER in arachis oil, once daily, 7 days/wk for 4 wks.

Results: At 10, 15 & 20mpk doses there were reduced body wt gains associated with reduced food intake. There was treatment-related ataxia and thinness & brittleness of long bones resulting in fractures. No histopathology was done.

b) Beadlet Formulation: Fullinsdorf rats (10/sex/gp) rec'd ER beadlet formul'n as a dietary admix at doses of 10, 15 & 20mpk/day. At the 2 higher doses, the expt. had to be terminated after 2-3 wks. Elevated alk. phos. was noted at 2 wks in all gps; at 4 wks, levels were still increased in the 10mpk gp.c) Micronized Form: Doses of 5, 10, 15 & 20mpk in M proved to be too high (wt loss, bone fracture & poor condition occurred), and the expt. had to be terminated after 12 days. In F, dose-related loss of wt & fractures occurred at 1-10mpk; the expt. was terminated within 2-3 wks. Clinical signs included inflammatory redness & stasis of the bladder and swelling of the penis (with urinary stasis). In F dosed at 1mpk, wt gain was slightly decreased and fractures were apparent after 3 wks.

Rats were most sensitive to the micronized form of ER.

d) Spray-dried Form: Fullinsdorf rats (10/sex/gp) were administered ER in the diet at doses of 1, 2.5, 5 & 10mpk/day, 7 days/wk for 4 wks. Doses of 1 & 2.5mpk were well-tolerated without any symptoms except for slightly lower body wt gain. A dose of 5mpk also affected wt gain and also produced inflammatory redness of bladder and fractures in several animals. At 10mpk, a definite loss of wt & extensive femoral fractures occurred along with redness of the bladder, hyperplasia of the spleen & clay-colored mottling of the kidneys. Additionally, skull bones of these rats appeared to be softer and the cranial sutures were less tight than those in rats of the lower dose gps or controls.#2. 13-Week Oral (gavage) in Rats (Report #83,759)

Done at Centre de Recherche et d'Elevage des Oncins (CREO), Lyon, France.

Material Tested: ER suspended in peanut oil

Animals: OFA (S-D offspring), SPF quality; 15/sex/dose

Dose Levels: 0, 2, 6, 12 & 20mpk/day ER orally (stomach tube), once daily, 7 days/wk for 13 wks. After 4 wks of treatment, 5/sex/dose were killed (interim sacrifice).

Results:

2mpk/day: Well-tolerated; blood glucose, serum urea & alk. phos. were slightly above control; LDH was somewhat lower. Histologically, there were no abnormalities.

6mpk/day: No mortality, but body wt was inhibited. Bone fractures occurred, and a slight inc. in alk. phos. probably due to metaplastic process in the bones. Histologically, changes in the spleen (hollow sinusoids, increase in megakaryocytes, absence of hemosiderosis) were possibly related to changes in peripheral blood.

12mpk/day: Mortality after 3 wks; body wt gain inhibited; blood chem. showed hemoconc'n plus elevated serum glucose, urea, alk. phos. There were bone fractures, and histologically, atrophy of the germinal epithelium of the testes & papillomatous acanthosis/hyperkeratosis of the stomach.

20mpk/day: (Terminated after 3 wks.) Mortality, inhibition of body wt gain; neutrophilia after 2 wks; lowered calcium serum levels; bone fractures; histology was the same as at 12mpk/day.

#3. 18-Month Oral (Dietary Admix) Toxicity of ER in Rats [Conducted by Institut Francais de Recherches et Essais Biologiques (IFREB), l'Arbresle, France.]

Animals: OFA (Sprague-Dawley) rats, 30 rats/sex/group

Test Material: Ro 10-9359 mixed in the diet, consumed by rats for 18 consecutive months.

Experimental Design:Daily Intake of Ro 10-9359

	<u>Rats</u>	<u>Rat Numbers</u>
Controls	30 Males 30 Females	500-529 550-579
Group I - 0.5 mg/kg/day	30 Males 30 Females	100-129 150-179
Group II - 1.0 mg/kg/day	30 Males 30 Females	200-229 250-279
Group III - 3.0 mg/kg/day	30 Males 30 Females	300-329 350-379

Observations:

Clinical: Body wts. and food consumption - weekly.

Eye Exam: All animals examined with ophthalmoscope ("Heine's") at pre-treatment and at 12 & 18 months.

Hematology & Blood Chemistry: 10 males + 10 females from control and high dose groups at 3, 6, 12, 15 & 18 months; additional 10 control rats/sex were examined in Month 3.

BSP Clearance Test & Urine Exam: 10 males + 10 females from control and high dose group at 3, 12 & 18 months.

Necropsy: All rats from all groups examined grossly. Organ wts. of all groups of rats surviving at termination.

Histopathology: 10 animals/sex/group at termination. Additionally, "altered organs" of prematurely sacrificed animals.

### Results:

Clinical: No treatment-related behavioural abnormalities.

Dentition: Growth of teeth was accelerated in high dose group.

Bone Fractures: Fractures were observed in one male of the mid dose group, and in about 50% of the high dose group. No fractures were noted in the low dose rats.

Body Weights/Growth Rate: Marked decrease in high dose males and females from week 6 onward. Slight decrease in mid dose females; normal in males of mid and low dose rats.

Food Consumption: Reduced in all treated females, but especially in high dose females; slight decrease in high dose males.

Hematology: Minimal reductions of RBC counts (8-13% less than controls) and hemoglobin conc. (5-11%) in high dose rats.

Occasional elevation of alkaline phosphatase in high dose male rats (compared to controls, 20% more at 6 mos. and 48% at 18 mos.); in the females between 30 and 73% more than controls from 6 mos.

Blood Chemistry, Ophthalmic & Urine Examination, and Organ Weights (at autopsy) revealed no alterations which would be related to administration of the test compound.

### Histopathology:

- There was no treatment-related effect on incidence of neoplasia.
- The majority of non-neoplastic lesions were randomly distributed across the groups in both sexes.
- A minimal increase in the incidence of hematopoietic hyperplasia in the spleens of the high-dose rats.

- A dose-related decrease in the incidence as well as severity of pigmentation of spleen in the mid- and high-dose males. In the females of the mid- and high-dose groups, a decrease in the severity of pigmentation was present.
- Discrete extramedullary hematopoiesis in the mesenteric lymph node in 2 males & 2 females of the mid-dose group and in 6 males & 3 females of the high-dose group.
- A high incidence of cystic endometrial hyperplasia of the uterus in high dose females.
- The lesion (hematopoiesis) in the spleen and mesenteric lymph node, according to the investigators, is "probably not related to the direct action of the compound on these organs, but is considered as a compensatory phenomenon".
- Testicular atrophy in 2/10 and 1/10 males in the mid- and high-dose groups.

#### #4. 4-Week Dietary Admix Oral Toxicity in Mice

Material Tested: Ro 10-9359/019 beadlets containing 15.8% substance administered as dietary admix.

Animals: Fullinsdorf albino mice; 20/sex/gp

Groups & Dosage: Mice were fed ER at daily doses of 2.5, 5, 10 & 20mpk; after 2 wks at 2.5 & 5mpk, doses were increased to 30 & 40mpk; total duration was 4 wks.

Results: After the second wk of testing, there was wt loss & indolence in the 20mpk gp. A marked wt loss was also seen at 30 & 40mpk. Changes such as increased osteoporosity & fractures did not become apparent before necropsy, and were found mainly in 20, 30 & 40mpk gps. F mice were more sensitive than M.

[In comparison, rats appeared to be twice as sensitive as mice. The reason for this difference may be in the shorter GI tract of mice and the resulting shorter time for absorption of the compound.]

#### #5. 13-Week Oral Toxicity in the Dog

Animals: Swiss "Laufhund"; 2 M + 2 F/dose level

Dose Levels: 3, 10, 30mpk in gelatin capsule, orally daily for 13 wks

Results:

- no mortality, but wt loss at the highest dose;

NDA 19-769

- dec. in sperm count in the testis & epididymis at all dose levels;
- dose-related changes in the coat (fur) of the animals, viz. alopecia, loss of hair pigment;
- hematology, blood chemistry, urine analysis, eye exams essentially normal;
- hyperplasia of the bone marrow in all gps, particularly pronounced at the HD;
- no evidence of effects on the bone which were seen in the rat study. (Effect in the rat may be related to the continuing growth of bones at the epiphyseal plate which occurs throughout life. This phenomenon does not occur in the dog.)

#6. 13-Week Oral Toxicity in (Puppy) Dogs Conducted by Laboratorium fuer Pharmakologie und Toxikologie, Prof. Dr. F. Leuschner, Hamburg, W. Germany

Objective: To provide background knowledge for clinical investigations in young patients.

Material Tested: Ro 10-9359/031 spray dried

Animals: Beagle dogs about 8 wks old; w/sex/gp

Groups: Controls & ER at dose of 5 mpk/day in capsule, once daily, 7 days/wk for 3 mos. (13 wks)

Lab Parameters: At pretest & wks 2, 6 & 13: hematology, blood chem., urinalysis. During wk 13: ophthalmoscopy, auditory, dentition & EKGs (before & 2 hrs after dosing)

Results: No mortality; the animals were alert and their general condition normal. Body wts, hematology, urinalysis, EKG's, ophthalmoscopic & auditory exam revealed no drug-related changes. SGOT was sig. elevated during wk 13, but normal up to wk 6; this change not considered to be drug-related.

Pathology: On gross or histologic exam, no lesions ascribed to drug treatment were reported.

The following is quoted verbatim from Dr. K. Teelman's internal report (No. B-86,936 dated 3/10/78).

#7. 12-Month Oral Toxicity of ER in Beagle Dogs (Conducted by Laboratorium  
Für Pharmakologie und Toxikologie, Hamburg, Germany.)

Material Tested: Ro 10-9359/031

Animals: Total of 32 Beagle dogs; 4 males + 4 females/dose level

Groups:

- I. Controls (placebo)
- II. 2.5 mg/kg/day - Low dose
- III. 5.0 mg/kg/day - Mid dose
- IV. 15.0 mg/kg/day - High dose

Ro 10-9359 in gelatin capsules was administered orally, once daily,  
for 52 weeks. Controls received cane sugar in capsules.

Body Weights & Food Consumption: weekly

Hematology & Blood Chemistry: pre-treatment, and at 13, 26, 39 & 52 weeks

Urinalysis, BSP Test, ECG, Eye & Hearing: pretest and at 26 & 52 weeks

Autopsy & Histoathology: all dogs

Results: The following abnormalities were noted:

2.5 mg/kg (Low-dose Group):

- slight and transient alopecia in 3/8 dogs;
- reduced flexibility of limb joint in one dog;
- no other abnormality.

5.0 mg/kg (Mid-dose Group):

- moderate alopecia in 4/8 dogs;
- stiff gait and occasional ataxia in 3 dogs; no abnormality of bone, joint, histologically in these dogs.
- moderate increase in erythrocyte sedimentation rate (ESR) at 26, 39, & 52 weeks.
- Testis: wt. decrease; slight diffuse testicular atrophy in 1 dog.

15.0 mg/kg (High-dose Group):

- in all dogs, alopecia of the whole body from 15-20 weeks onward;
- stiff gait and occasional ataxia; histologically hyperkeratosis in one dog;
- reduced Hb concentration and hematocrit;
- acceleration of ESR;
- slight elevation of SGPT;
- Testis: reduced wt. and atrophy histologically.

Histopathology:

2.5mpk/day: no drug-related findings

5mpk/day: slight diffuse canalicular atrophy of testes in one dog

15mpk/day: testicular atrophy combined with inhibited "spermiogenesis" in one dog; in another, cortical massive diffuse calcareous nephrosis; 2 dogs had amyloid deposits in the vascular wall of the thymus, and one of these had amyloids in several other organs as well. Particular attention was paid to skin, bone & joint changes, but with the exception of some hyperkeratosis in one dog, no pathological changes were observed.

## CARCINOGENICITY

#1. 2-Year Oral (Dietary Admix) Carcinogenicity Study in Rats with ER  
[Conducted by IFREB, France.]

Report No: 4222 dated 5/27/80; study conducted from 6/77-6/79

Animals: OFA (Sprague-Dawley) rats; 50 rats/sex/group; controls 100/sex

Test Material: Ro 10-9359 mixed in the diet consumed by rat for 24 mos.

Experimental Design:Daily Intake of Ro 10-9359

	Rats	Rat Numbers
Controls	100 Males	500-599
	100 Females	600-699
0.5 mg/kg/day (Low Dose)	50 Males	100-149
	50 Females	150-199
1.0 mg/kg/day (Mid Dose)	50 Males	200-249
	50 Females	250-299
3.0 mg/kg/day (High Dose)	50 Males	300-349
	50 Females	350-399

Dose levels are expressed as active substance Ro 10-9359.

Observations:Clinical: daily; body wts. and food consumption - weeklyPost Mortems: gross exam of all rats of all groups which died spontaneously or were sacrificed at termination.Histopathology: performed on 20/animals/sex of controls and high dose rats (called "systematic" examination). All organs and tissues with masses or other abnormality detected on gross exam (called "non-systematic" exam). Also those organs significantly affected in high dose animals. were examined in 20 animals/sex in the low- and mid-dose treated groups.HISTOLOGICAL EXAMINATIONS

- listed organs on 20 animals/sex of the control and group III
- Selection of animals
  - more than 20 animals sacrificed at the end of the trial : numerical order.
  - less than 20 animals sacrificed at the end of the trial : those sacrificed, others being selected among the last ones which were sacrificed during the experiment by backward chronological order until a total of 20 is reached.
- Those organs significantly affected in group III were systematically examined in 20 animals/sex of groups I and II.
- Tumours were systematically examined whether in animals sacrificed at the end of the trial or those sacrificed during the course of the study.

**"Systematic" Study:** All organs in 20 rats/sex of controls & HD

**"Non-Systematic" Study:** Remaining animals sac'd or found dead during the course of the study.

**Results:**

**Mortality:** Comparable in treated and control groups.

**Body Weight:** Slight reduction in body wt. gain in males of the high-dose, and females in the mid- and high-dose groups.

**Food Consumption:** Slight reduction in high-dose males and females.

**Bone Fractures:** Increased frequency of fractures of the long bones in males (20%) and more pronounced in females (50%) of the high dose group only. It was not observed in mid- and low-dose rats.

**Dentition:** Accelerated growth of the incisor teeth in some males and more pronounced in females of the high dose group only. It was not observed in mid- and low-dose rats.

**Histopathology:**

**Neoplastic:**

- In the treatment groups belonging to "systematic" or "non-systematic" study, the incidence of tumor bearers for pituitary, thyroid, adrenals, mammary gland and uterine polyp was comparable to that in the control and did not reveal statistically significant differences.

**Non-neoplastic Lesions:**

- In both sexes, there was no significant difference either in the "systematic" or "non-systematic" studies for heart fibrosis, liver biliary hyperplasia, fatty cysts (fatty degeneration) and hyperplasia of the adrenals. These were considered senile changes.
- Arteritis or periarteritis (of the periarteritis nodosa type) of the mesentery, considered to be related to old age, was found in several animals, especially in control M. The frequency of this lesion was markedly reduced in the treated rats in a dose-related fashion.
- In the systematic and non-systematic studies, high-dose females had a significant treatment-related decrease in the incidence of foamy macrophages in the lungs.

- In the systematic study, high dose males had a significant decrease in the incidence of glandular ectasia (dilatation) of the stomach.
- In the systematic study, there was a treatment-related significant decrease in the deposition of the pigment in the spleen of high dose male and female rats.
- In the systematic study, a significant increase in the incidence of hematopoiesis in the mesenteric lymph node in the male and female rats of the high dose group was considered to reflect an indirect compensatory effect.

Frequency of lesions is listed in NDA Vol. 1.127, pp. 3-25 (pp. 254-276 of report).

No skin lesions were reported.

## #2. 80-Week Oral (Dietary) Carcinogenicity Study in Mice

Roche Report No. B-104'088

Conducted by Hazleton Labs, Europe (HLE) Ltd., Harrogate, North Yorkshire, England; Hazelton Report No. 3347-161/57 dated January 1984

Preliminary Study: An anticipated oral HD of 6mpk/day was tested in 9 M + 9 F CD-1 mice for 4 wks. Treated mice showed slightly reduced wt gains (more marked in F), slight reduction of food intake in F and slightly increased rel. liver & kidney wts. The recommended doses for carcinogenicity study: 1, 3 & 5mpk/day.

### Main Study:

Material Tested: Ro 10-9359/033 - Tigason Pulver 25% Spray-dried

Animals: CR CD-1 (ICR) BR strain Swiss mice; 51 M + 51 F/gp

<u>Groups &amp; Doses:</u>	<u>Formulation</u>	<u>Active Ingrid.</u>	<u>Wk of Study</u>
1. Control	0	0	1-80
2. Low Dose	4	1	1-80
3. Mid Dose	12	3	1-26
	0	0	27-30
4. High Dose	8	2	31-80
	20	5	1-26
	0	0	27-30
5. Control	16	4	31-80
	0	0	1-80

Note: In Groups 3 & 4, mice were not dosed for 4 wks (27-30) and beginning wk 31, dose was reduced to 2 & 4mpk/day.

**Husbandry:** The mice were kept in cages with sawdust, 3/cage, and exposed to fluorescent light 12 hrs/day.

**Histopathology:** All tissues from all animals in Gps 1, 4 & 5, and from all mice dying prematurely in gps 2 & 3. Tissues from survivors at terminal kill were restricted to tissue masses and all gross lesions suspected of being tumors.

**Results:** [Please refer to table above for gps (Control, LD, MD & HD) & doses corresponding to gp numbers mentioned below.]

**Group 2:** Survival of F in this gp was sig. reduced ( $p < 0.05$ ). There was no evidence of impaired mobility; organ wts were comparable to those in controls; no definite treatment-related neoplastic or non-neoplastic changes.

**Group 3:**

- Survival rate in F was comparable to that in controls. In the M, however, differences occurred after wk 62. Between that time and the terminal kill, 19 M with skin lesions were sac'd for humane reasons. This resulted in only 39% survival rate at termination, which was sig. lower ( $p < 0.001$ ) than 69% & 73% in the 2 control gps.
- Clinical Signs: Impaired mobility starting at wk 17 in F & wk 19 in M and skin lesions (ulcerative dermatitis), more prevalent in M.
- Food Intake: In M, comparable to controls, but in F, slightly less (13%). Body w gain in either sex was markedly and sig. lower ( $p < 0.01$ ) than in controls.
- The mean relative kidney wts in Gp 3 M were 7% or 10% higher than the two control gps, the larger inc. (compared to Gp 5) achieving stat. sig. ( $p < 0.01$ ). F also had increases of 10% or 19%, both stat. sig. ( $p < 0.01$ ). However, abs. kidney wts of both sexes were similar to or marginally lower than those in controls. No wt changes occurred in other organs.
- Pathology: No definite treatment-related neoplastic or other histologic changes occurred. The incidence of blood vessel tumors in M (3 non-fatal, 1 fatal) was comparable to that of Gp 5 M (2 non-fatal, 1 fatal).

(Note: Histopathology was limited in this gp; vide supra.)

**Group 4:**

- Survival Rate: In M, comparable to control until wk 62, but at termination, only 37% of the M were alive compared to 73% or 69% in controls - stat. sig. ( $p < 0.001$ ) - attributed to either skin lesions or impaired mobility. Note that only 5 M in Gp 4 were killed due to skin lesions, compared to 19 in Gp 3.

- In F, survival rate was reduced early in the study (on wk 64, only 55% were alive), and this dec. could be related to bone or joint lesions cited as cause of death in 25/31 mice which were killed or died spontaneously prior to termination (i.e., the reason for preterminal killing was bone/joint disease in F and skin lesion in M).
- Clinical Signs: Skin lesions in M and bone/joint disease in F, resulting in impaired mobility.
- Food Intake; Body Wt Gain: Severely reduced - much more so than in Gp 3.
- Organ Wts: The mean rel. kidney wts of M & F were sig. greater (like Gp 3) than controls, but abs. kidney wts were sig. lower than controls.
- Pathology: The incidence of blood vessel tumors was higher in M, but not F. In 8 M, the incidence was stat. sig. On the other hand, there was apparent reduction in total incidence of lung tumors in both sexes.

Comment: This was the only treated gp in which all tissues from all animals were examined histologically.

[Note: Incidence of morbidity & mortality (Table 8 of report) and tumor incidence (Tables 10 & 11 of report) are appended to this review.]

Conclusions: The low dose (Gp 2) was well tolerated, but at higher dose levels (Gps 3 & 4), clinical signs of toxicity (decreased food intake & body wt gain, impaired mobility, alterations of the skeletal system, such as distortion of the spine & fracture of the long bones) which are typical of retinoid toxicity.

The prevalence of skin lesions (ulcerative dermatitis in Gps 3 & 4) occurred mostly in M, and the incidence does not appear to be dose-related. The incidence in M was 9/21, 19/32 & 5/34 in Gps 2, 3 & 4, respectively. According to the investigators, fighting among M was considered to be the etiology; the fact that impaired mobility probably reduced fighting may have resulted in the lower incidence in Gp 4 M. Among the drug-treated F, it occurred in 3/15 in Gp 3.

Commenting on neoplastic lesions, the investigators state: "The incidence of blood vessel tumours in HD M was slightly higher than would be expected from historical control data and, where tumours at different sites were pooled, this incidence could be shown to be stat. sig. higher than that of the concurrent controls groups. In contrast, the incidence of lung tumors in Gp 4 appeared to be reduced. However, this was not stat. sig. when the data were adjusted for survival. The interpretation of the increased yield of blood vessel tumors in terms of oncogenicity of the compound remains uncertain. The total number of tumors was small, only one sex was involved, and the dose level was sufficiently high to cause clear evidence of toxicity. There is also a published report of reduced blood vessel tumor incidence following retinoid administration in the rat." [Kamm, J.J. J. Amer. Acad. Dermatol. 6: pp. 652-659, 1982.]

[For skin lesion, see Williams, L. & Elias, M. Arch. Derm. 117: 611-619, 1981. Nature of skin fragility in patients receiving retinoids for systemic effect.]

Plasma Conc'n of Unchanged Drug & Main Metabolite (Ro 10-1670)

(Report No. B-94'236 by Dr. U. Paravicine)

ER was absorbed during the 80-wk study period to an increasing amount with increasing dose. Parent drug was rapidly hydrolyzed to its main metabolite (Ro 10-1670), leading to very low ER conc'n in plasma (4-16ng/ml) and to considerably high Ro 10-1670 conc'n (12-121ng/ml). Conc'ns increased with increasing dose, but not with increasing study time. From this plasma conc'n monitoring, no hint was given of accumulation of drug in the body. For plasma conc'n of ER & its metabolite, please see Table & Figure in the appendix.

#3. The Influence of Topical & Oral Retinoid Treatment on Photocarcinogenesis in Hairless Albino Mice (H.R. Hartmann & K. Leutmann in "Retinoids", pp. 447-451, Springer-Verlag, 1981)

Three gps of 40 mice were irradiated & dosed orally (intubation) with placebo or ER @ 0.5 & 1.5mpk, 5x/wk x30 wks, and radiated 3x/wk x28 wks, beginning 2 wks after commencement of dosing. ER did not enhance tumor formation. Histologically, tumors were similar in all irradiated gps.

MUTAGENICITY

#1. Ames Test

- a) Using tester strains TA 1535 (base pair substitution), 1537 (frame shift) & 1538 (frame shift), negative results were reported at conc'ns of ER of 10 & 50ug/plate.
- b) Using tester strains TA 98 & 100 and E. coli WP2 uvr<sup>-</sup>, no mutagenicity of ER was found in either the absence or presence of rat liver S-9 fraction at 10, 50, 500 & 4000ug/plate with S. typhimurium TA 98 & E. coli WP2 uvr<sup>-</sup>. Using strain TA 100, a weak but sig. (p less than 0.01) mutagenic activity was observed without metabolic activation (i.e., without S-9 rat liver fraction) at 1000, 2000 & 4000ug/plate.

[Done by S. Itoh et al., NNRC (Roche, Japan) Memo dated 3/26/81]

#2. Host-Mediated Assay: (Methodology of Legator & Malling) Fullinsdorf albino mice (4 M + 4 F/dose gp) used as host animals; S. typhimurium strains TA 1530, 1532 & 1964 served as indicator organisms. Suspensions of ER in rape oil were administered orally. At the same time, each animal received 2mg of a 90-min. culture of the corresponding bacterial strain injected into the peritoneal cavity. After 3 hrs, mice were sacrificed, the bacteria retrieved and plated on minimal medium where only his<sup>-</sup> or his<sup>+</sup> could grow. At dose levels of 250, 500 & 1000mpk body wt, ER yielded negative results.

#3. Micronucleus Test: 3 M + 3 F Fullinsdorf mice/gp were administered ER orally twice, at dose levels of 250, 500 or 1000mpk. Bone marrow smears from the femur of treated mice were stained and micronuclei were counted in the erythrocytes (4000 RBCs/animal). Results were negative. The average % of erythrocytes containing one or more micronuclei was 0.054 + 0.02 in controls and 0.050, 0.054 & 0.050 (all with SE + 0.002) for 250, 500 & 1000mpk gps, respectively.

#4. In vitro tests in bacteria with ER in combination with UV light were negative (see Hummler & Shupbach, Retinoids in C.E. Orfanos et al. (ed) pp. 49-59 Springer-Verlag, 1981).

#5. Mutagenicity Evaluation of ER with Saccharomyces cerevisiae D-7 Strain (Research Report No. B-104 844 dated 1/25/84)

With ER at conc'ns ranging from 0.01-10ug/ml, no mutagenic activity was reported.

#6. Cytogenic Studies in Patients

a) Bounaneaux, Y: Influence of etretinate on sister chromatid exchange (SCE) of human lymphocytes

The rate of SCE's in 6 control & 10 patients were comparable.

b) Happle R. & Niedworck, N. In Orfano's "Retinoids", pp. 61-65

Nine patients were treated with ER at daily doses of 0.5-1mg/kg for 4-21 wks; there were 9 controls. There was no effect on chromosomal breakage; the frequency of aberrant metaphases varied from 0-4.3% in the controls and 0.8-4.7% in the treated patients.

c) Obe, G. & Tsambaos (Retinoids pp. 67-70)

Investigation of chromosomal aberration (SCE) in human lymphocytes was done in psoriatic patients under treatment with ER at 25-75mg/day for 4-24 wks. The frequency of exchange-type aberrations was found to be at the control level. In 8 patients, no elevation of the rate of SCE was reported.

d) Juhl et al. Mutation Res. 5: 317-320, 1978

In this in vitro expt. with human fibroblast, there was a dose-related increase in SCE metaphases when ER was added to the culture medium. The response was similar to that of vitamin A acid (presumably all trans retinoic acid).

## REPRODUCTION

# 1. Fertility & General Reproduction in Rats (Segment I) (Conducted by Reproto in Germany)Methodology:

Animals: Albino, SPF rats (strain specified) from Hoffman-La-Roche Labs in Germany

Treatment: Ro 10-9529, suspended in oil, was administered at doses of 1.0, 2.5 or 5.0 mg/kg/day orally, by intubation, according to the following schedule. Controls received oil.

Males: 35 males at each dose level were dosed from 70 days prior to mating and continued during the 14-day mating period.

Females: 31-35 females/dose level received the drug from 14 days prior to mating, during the 14-day mating period, and treatment continued in mated females up to 14 days p.c.

Procedure: Males were killed at the end of the mating period.

Treated & pregnant females:

- a) From each dose group 1/2 of the females were sacrificed on day 14 p.c. and various reproductive parameters evaluated.
- b) The remaining 1/2 females of each dose group were allowed to deliver. F<sub>1</sub> pups were evaluated at 23 days of age.
- c) F<sub>1</sub> pups were raised and evaluated at 65 days of age.
- d) F<sub>1</sub> males & females were mated. At the end of the 14-day mating period, the F<sub>1</sub> males were killed and evaluated. The mated females were allowed to give birth and the F<sub>2</sub> generation pups were evaluated at 23 days of age. Also, the F<sub>1</sub> mothers were evaluated on day 23 post-partum.

Note: Pups of F<sub>1</sub> and F<sub>2</sub> generation did not receive treatment with the drug.

Results:

1.0 & 2.5 mg/kg: All reproductive parameters in the low and mid-dose groups were comparable to those in the controls.

5.0 mg/kg: Rats in the high dose group were affected. Mating index (mean mating period/animal) in F-generation females was prolonged (4.8 days in treated vs. 3.0 days in controls).

There was decreased post-natal viability of the F<sub>1</sub> pups.

# Embryotoxicity in the Rat: (Segment II Teratology)

Conducted by Reprotox, Münster, Germany

Animals: SPF albino rats from Hoffmann-La Roche.Treatment: Controls, 2 mg/kg, 4 mg/kg, 8 mg/kg of Ro 10-9359 per day, orally by intubation from 7th to 16th day of gestation.

Fetuses obtained by caesarian section on 21st day of pregnancy.

Results: RATS:

	<u>Ro 10-9359</u>			
	<u>Controls</u>	<u>2 mg/kg</u>	<u>4 mg/kg</u>	<u>8 mg/kg</u>
No. pregnant rats	16	18	16	23
Total fetuses	148	149	155	216
Live fetuses	148	149	154	215
<u>No. affected/No. examined (% affected)</u> :				
Externally visible malformations (%)	0/48	0/149	1/155 (0.6%)	12/216 (5.6%)
Skeletal malformations	0/85	0/84	0/101	1/126
Skeletal variations	10/85 (11.8%)	54/84 (64.3%)	78/101 (77.2%)	101/126 (80.2%)
Visceral malformations	0/63	3/65 (4.6%)	0/54	46/90 (51.1%)
<hr/>				
No. of pregnant rats used for rearing offspring (birth to 23 days of age)	11	9	10	10

Dams: No effect on body weights or behaviour.

Fetus: 2 mg/kg and 4 mg/kg group:

- (1) increased incidence of skeletal variations (64.3% and 77.2% compared to 11.8% in controls)
- (2) increased mortality rate in the offspring.

8 mg/kg group:

- (1) increased incidence of visceral malformation in addition to higher skeletal variation.
- (2) marked rise in the stillbirth rate
- (3) over 50% mortality among offspring which were born alive but died post-natally.
- (4) The teratogenic effects reportedly correspond to "vitamin A type" effects on the fetus (presumably the types of fetal anomalies were similar).

Teratogenic threshold dose in the rat appears to be below 2 mg/kg, p.o.

### 3. Modified Segment II Teratology Studies in Rats

(Conducted by Roche Labs, Nutley, NJ.)

Purpose: ER at doses of 2, 4 & 8mpk/day was administered orally (intubation) from days 6-15 of gestation. At doses of 2 & 4mpk/day, no treatment-related malformations were noted, although the incidence of skeletal variations was increased. At 8mpk/day, vitamin-A type malformation (exencephaly, anophthalmia, cleft palate) were observed.

Two studies were performed using pregnant CR-CD rats. Methodology was similar to that used for the usual teratology studies, except that the frequency and stage of gestation varied. Rats were necropsied on day 20 and evaluated for the usual reproductive/terata evaluation.

#### a. Single Dose Admin. on Day 8 of Gestation (GCR-N-36542 dated 11/11/82)

This study was designed to observe dose-related curve for malformations following a single-dose exposure on day 8 (the earliest time when the rat is susceptible to teratogenesis).

Groups: Vehicle controls, F. at doses of 1, 3, 6, 10, 15 & 25mpk/day. The dose was administered once only on day 8 of gestation.

#### Results:

- Doses of 1, 3 & 6mpk/day were not teratogenic.
- Doses of 10, 15 & 25mpk/day produced treatment-related increased resorption & fetal abnormality, as well as reduced fetal wts. These doses were both embryotoxic (increased resorp. rate & decreased fetal wts) and teratogenic.

#### Plasma Conc'n of ER & 3 Metabolites in Rats after Single & Multiple Doses (Rpt. # N-122879 dated 5/3/84; Vane et al.)

Plasma conc'n of ER & its metabolites was determined in the rat during the 24-hr post-dosing period following oral admin. of a single dose of

5, 10 or 25mpk on gestation day 8, or following multiple dosing (daily for 3 wks) with 10mpk/day of ER. There was a dose-related inc. in both the area under the 24-hr plasma conc'n curve (AUC) and in the peak plasma levels of ER and its primary metabolites. It was also noted that within 24 hrs following either single or multiple dosing, the plasma conc'n of ER and its major metabolites were reduced to levels below those expected to produce teratogenesis.

**b. Single Dose on Gestation Days 6, 7 or 8** (ECR N-10276 dated 2/24/84)

**Purpose:** Gestation day 8 is considered to be the earliest embryonic period when the rat is susceptible to retinoid teratogenesis. Typical hypovitaminosis-A teratogenesis did not occur with treatment of an otherwise teratogenic dose (20mpk) of all-trans retinoic acid on gestation days 0, 2, 4, 6 or even 7, even though treatment on day 8 produced ED<sub>01</sub> fetal abnormality rate in rats (Hostler, A. Teratology 23: 25-31, 1981).

Previously (Study a.) a single dose of 10 or 25mpk/day of ER on day 8 of gest. was teratogenic. This study (b.) was done to test the hypothesis that teratogenicity should not occur following treatment on day 6 or 7, but will on day 8; the latter will serve as pos. control.

Plasma conc'n of the drug or its metabolite were very low following a single dose within 24 hrs.

**Animals:** 10 pregnant F rats/group

<u>Group</u>		<u>Dose (mg/kg)</u>	<u>Treated on Gestation Day</u>
A	Vehicle Controls	0	
B	Ro 10-9359	10	6
C	"	25	6
D	Vehicle Control	0	7
E	Ro 10-9359	10	7
F	"	25	7
G	Vehicle Control	0	8
H	Ro 10-9359	10	8
I	"	25	8

**Results:**

- Treatment of pregnant rat on gest. day 8 with 10 or 25mpk of ER produced an embryotoxic (increased resorp. rate) and teratogenic response in the litters of treated dams. This was expected.
- Treatment with the same doses (10 or 25mpk) administered on day 6 or 7 was neither embryotoxic nor teratogenic.
- Plasma conc'n of ER given on gest. day 6 or 7 should have fallen to levels below those expected to produce an embryotoxic response.

- A relationship between occurrence of teratogenic potential and levels of ER and its major metabolites in maternal plasma was established.

**14. Reproduction (Embryotoxic and teratologic) Study in Mouse: Performed by Reprotox, Münster, Germany.**

23 albino, SPF mice obtained from Hoffmann-LaRoche; sperm positive/vaginal plug - Day 1; dose - 1 mg/kg orally and daily from 8th to 10th day of pregnancy; expt. terminated on Day 19; fetuses observed grossly; skeletons further examined after alizarin staining.

**Results:**

- (a) Decrease in the mean body weight gain of the dams;
- (b) No drug related skeletal anomalies in the fetuses.

**Comment:**

- (a) Apparently fetuses were not sectioned for anomalies of the viscera.
- (b) Treatment period is shorter
- (c) The study has not followed our guidelines for teratology.

**15) Embryotoxicity in the Mouse: (Segment II Teratology)**

Conducted by Reprotox, Münster, Germany.

**Animals:** SPF albino mice from Hoffmann-La Roche.

**Treatment:** Controls, 2 mg/kg, 4 mg/kg, and 8 mg/kg body weight of No 10-9359, orally by intubation. Treatment administered from 7th day to 16th day of gestation.

Used 9 to 13 pregnant mice per group for teratology, and 11 to 14 pregnant mice per group for the rearing of the offspring experiment.

For teratology experiment fetuses were obtained by caesarian section on 19th day of gestation.

**Results:**

- (i) 2 mg/kg dose had no effect on the fetus.
- (ii) 4 mg/kg and 8 mg/kg doses had pronounced embryotoxic and teratogenic activity. Type of malformations corresponded to those by hypervitaminosis A.
- (iii) Embryotoxic threshold dose in the mouse was considered to be between 2 and 4 mg/kg, orally.
- (iv) Plasma concentrations were the same with 4 mg/kg dose in the mouse as with 2 mg/kg in humans (therapeutic dose intended for human: 4 x 25 mg capsules/day).

**95. Embryotoxicity in the Rabbits: (Segment II Teratology)**

**Animals:** Silver rabbits (Füllinsdorf Animal Farm)

**Treatment:** 0, 0.5, 1, 2 mg/kg/day, orally by intubation from 7th to 19th day of pregnancy.

**Results:**

- (i) 0.5 mg/kg and 1.0 mg/kg had no effect on reproductive parameters.
- (ii) At 2 mg/kg the drug was teratogenic (therapeutic dose in humans = 2 mg/kg).
- (iii) Following a single dose plasma concentration yielded 5-20 times lower blood values when compared with corresponding experiments in humans. On calculation of the base blood levels 1/5 to 1/20 of the dose intended for humans is thus teratogenic in the rabbit. Thus, it seems the rabbit as a species is more sensitive to teratogenesis with this drug.

**96. Perinatal and Postnatal Studies in the Rat (Segment III):**

Conducted by Reprotox, Münster, Germany.

**Animals:** SPF albino rats obtained from Hoffmann-La Roche. Sperm positive day = Day 1. About 27 pregnant female rats per group.

**Experimental Design:** 0, 2, 4, and 8 mg/kg/day of Ro 10-9359 orally by intubation. Treatment from 16th day post coitum to 23rd day post partum.

**Results:**

- (i) Dosage of 2 mg/kg and 4 mg/kg had no effect on the dam or the fetus
- (ii) 8 mg/kg dose was fetotoxic ("all the damage to the fetus"), and at this dose level the treatment seemed to have inhibiting effect on weight gain and chance of survival.