CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-662 / S-038

Trade Name: Accutane

Generic Name: (isotretinoin)

Sponsor: Hoffman La Roche Inc.

Approval Date: May 1, 2000

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APPLICATION NUMBER:

18-662 / S-038

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-038

APPROVAL LETTER

162.1

NDA 18-662/S-038

Hoffmann-La Roche Inc.
Attention: Betty Holland, M.S.
Program Director
340 Kingsland Street
Nutley, New Jersey 07110-1199

MAY 1 2000

Dear Ms. Holland:

Please refer to your supplemental new drug applications dated September 10, 1999, received September 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) Capsules, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated December 22, 1999; and January 17 and 26, February 18 and 24, and April 6 and 18, 2000.

This supplemental new drug application provides for revisions to the labeling regarding the use of contraceptive methods.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-662/S-038." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

5/1/00

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-038

APPROVED LABELING

APPROVED

MAY 1 2000

Roche

ACCUTANE®
(isotretinoin)
CAPSULES

Avoid Pregnancy

CONTRAINDICATIONS AND WARNINGS: Accutane must not be used by females who are pregnant or who may become pregnant while undergoing treatment. Although not every fetus exposed to Accutane has resulted in a deformed child, there is an extremely high risk that a deformed infant can result if pregnancy occurs while taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. Presently, there are no accurate means of determining after Accutane exposure which fetus has been affected and which fetus has not been affected.

Accutane is contraindicated in females of childbearing potential unless the patient meets all of the following conditions:

- **must have severe disfiguring nodular acne that is recalcitrant to standard therapies (see INDICATIONS AND USAGE for definition)**
- **must be reliable in understanding and carrying out instructions**
- **must be capable of complying with the mandatory contraceptive measures required for Accutane therapy and understand behaviors associated with an increased risk of pregnancy**
- **must have received both oral and written warnings of the hazards of taking Accutane during pregnancy and exposing a fetus to the drug**
- **must have received both oral and written information on the types of contraceptive methods and warnings about the rates of possible contraceptive failure, and of the need to use two separate, effective forms of contraception simultaneously, unless abstinence is the chosen method, or the patient has undergone a hysterectomy and has acknowledged in writing her understanding of the information and warnings and of the need for using two contraceptive methods simultaneously**

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- must have had a negative urine or serum pregnancy test with a sensitivity of at least 50 mIU/mL when the patient is qualified for Accutane therapy by the prescriber, and must have had a second negative urine or serum pregnancy test on the second day of the next normal menstrual period or at least 11 days after the last unprotected act of sexual intercourse, whichever is later

- must understand and agree that her prescriber will issue her a prescription for Accutane only after she has contacted the prescriber to confirm that she has obtained a negative result for the second urine pregnancy test which is to be conducted on the second day of the next normal menstrual period or at least 11 days after the last unprotected act of sexual intercourse, whichever is later

- must have received instruction to join the Accutane Survey and have watched a videotape, provided by Roche to her prescriber, that provides information about contraceptive methods, possible reasons for contraceptive failure, and importance of using effective contraception when taking teratogenic drugs.

Major human fetal abnormalities related to Accutane administration have been documented: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); skull abnormality; external ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); cardiovascular abnormalities; facial dysmorphia; cleft palate; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted. Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported. There is an increased risk of spontaneous abortion. In addition, premature births have been reported.

It is strongly recommended that a prescription for Accutane should not be issued by the prescriber until a female patient has had negative results from two urine or serum pregnancy tests, one of which is performed in the prescriber's office when the patient is qualified for Accutane therapy, the second of which is performed on the second day of the next normal menstrual period or 11 days after the last unprotected act of sexual intercourse, whichever is later. It is also recommended that pregnancy testing and counseling about contraception and behaviors associated with an increased risk of pregnancy be repeated on a monthly basis. To assure compliance, the prescriber should not issue a prescription for a female patient, until after the second negative pregnancy test result is obtained. In addition, the prescriber should prescribe no more than a 1-month supply of the drug for all Accutane patients and no automatic refills should be permitted. Roche will supply urine pregnancy test kits for female Accutane patients for the initial, second, and monthly testing during therapy.

Effective contraception must be used for at least 1 month before beginning Accutane therapy, during therapy, and for 1 month following discontinuation of therapy even

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where there has been a history of infertility, unless due to hysterectomy. The patient must be counseled about and understand the limitations of any chosen contraceptive method. The patient must also understand the risks associated with not using two contraceptive methods, even when one of the chosen methods is a hormonal contraceptive method.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, even when one of the forms is a hormonal contraceptive method. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane.

If a pregnancy does occur during treatment, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are encouraged to report all cases of pregnancy with specific information about the contraceptive forms used during Accutane therapy and for 1 month following therapy, either to the Roche Medical Services @ 1-800-526-6367 or to the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

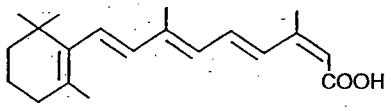
Accutane should be prescribed only by prescribers who have special competence in the diagnosis and treatment of severe recalcitrant nodular acne, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity if Accutane is used during pregnancy.

Prescribers who prescribe Accutane should use the Pregnancy Prevention Program℠ kit provided by Roche for the counseling of patients, should instruct the patient to participate in the Accutane Survey, and should receive medical education sponsored by Roche about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy.

DESCRIPTION: Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and 40-mg soft gelatin capsules for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow-orange to orange crystalline powder with a molecular weight of 300.44. The structural formula is:

ACCUTANE® (isotretinoin)



CLINICAL PHARMACOLOGY: Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 2.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of Accutane is unknown.

Nodular Acne: Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with Accutane, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.[1]

Pharmacokinetics: *Absorption:* Oral absorption of isotretinoin is optimal when taken with food or milk. After administration of a single 80-mg oral dose (two 40-mg capsules) of isotretinoin to 15 healthy male subjects, maximum blood concentrations ranged from 167 to 459 ng/mL (mean 256 ng/mL) and were achieved in 1 to 6 hours (mean 3.2 hours). The oral absorption of isotretinoin is consistent with first-order kinetics and can be described with a linear two-compartment model. Nodular acne does not alter the absorption of the drug: In a 27-day study of isotretinoin in 10 male patients with nodular acne treated with an oral dose of 40 mg bid, the mean peak concentration ranged from 98 ng/mL to 535 ng/mL (mean 262 ng/mL) and occurred at 2 to 4 hours after administration (mean 2.9 hours). In these patients, the mean ± SD minimum steady-state blood concentration of isotretinoin was 160 ± 19 ng/mL. The terminal elimination half-life was consistent with that observed in normal subjects.

Distribution: Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism: After oral administration of isotretinoin, 4-*oxo*-isotretinoin is the major metabolite identified in the blood. Maximum concentrations of 4-*oxo*-isotretinoin (87 to 399 ng/mL) were achieved at 6 to 20 hours after oral administration of two 40-mg capsules; the blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours. Isotretinoin also undergoes isomerization to the all-trans-isomer, tretinoin, which is then metabolized to its corresponding 4-*oxo*-metabolite; both have been detected. Both parent compound and metabolites are further metabolized into conjugates which are excreted.

Elimination: Following administration of an 80-mg liquid suspension oral dose of ^{14}C-isotretinoin, ^{14}C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). The terminal elimination half-life of isotretinoin ranges from 10 to 20 hours. The mean elimination half-life of 4-*oxo*-isotretinoin is 25 hours (range 17 to 50 hours). After both single and multiple doses, the accumulation ratio of 4-*oxo*-isotretinoin to parent compound is 3 to 3.5.

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INDICATIONS AND USAGE: *Severe recalcitrant nodular acne:* Accutane is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition,[2] means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, for female patients of childbearing potential, Accutane is indicated only for those females who are not pregnant (see boxed CONTRAINDICATIONS AND WARNINGS).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.[1,3,4] If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off Accutane. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see WARNINGS: *Skeletal: Hyperostosis* and *Premature Epiphyseal Closure*).

CONTRAINDICATIONS: Pregnancy: Category X. See boxed CONTRAINDICATIONS AND WARNINGS.

Allergic Reactions: Accutane is contraindicated in patients who are hypersensitive to this medication or to any of its components. Accutane should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule (see PRECAUTIONS: *Hypersensitivity*).

WARNINGS: *Psychiatric Disorders:* Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS: *Psychiatric*).

***Pseudotumor Cerebri:* Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Accutane immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS: *Neurological*).**

Pancreatitis: Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. **In rare instances, fatal hemorrhagic pancreatitis has been reported.** Accutane should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

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Lipids: Elevations of serum triglycerides have been reported in patients treated with Accutane. Marked elevations of serum triglycerides in excess of 800 mg/dL were reported in approximately 25% of patients receiving Accutane in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects on triglycerides, HDL, and cholesterol were reversible upon cessation of Accutane therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane.[5]

Blood lipid determinations should be performed before Accutane is given and then at intervals until the lipid response to Accutane is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk during Accutane therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Accutane therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS: *Laboratory Tests*).

The cardiovascular consequences of hypertriglyceridemia associated with Accutane are unknown. *Animal Studies*: In rats given 8 or 32 mg/kg/day of isotretinoin (0.7 or 2.7 times the maximum clinical dose after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (15 to 30 times the maximum clinical dose, respectively, after normalization for total body surface area).

Hearing Impairment: Impaired hearing has been reported in patients taking Accutane; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not been established. Patients who experience tinnitus or hearing impairment should discontinue Accutane treatment and be referred to specialized care for further evaluation (see ADVERSE REACTIONS: *Special Senses*).

Hepatotoxicity: Clinical hepatitis considered to be possibly or probably related to Accutane therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment with Accutane, the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease: Accutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Accutane

treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see ADVERSE REACTIONS: *Gastrointestinal*).

Skeletal: *Hyperostosis*: A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization.[6] Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Accutane treatment courses for acne are unknown.

Premature Epiphyseal Closure: There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses, but it is not known if there is a causal relationship with Accutane. In clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day, two children showed x-ray findings suggestive of premature epiphyseal closure. The skeletal effects of multiple Accutane treatment courses for acne are unknown.

Vision Impairment: Visual problems should be carefully monitored. All Accutane patients experiencing visual difficulties should discontinue Accutane treatment and have an ophthalmological examination (see ADVERSE REACTIONS: *Special Senses*).

Corneal Opacities: Corneal opacities have occurred in patients receiving Accutane for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients treated with Accutane have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug (see ADVERSE REACTIONS: *Special Senses*).

Decreased Night Vision: Decreased night vision has been reported during Accutane therapy and in some instances the event has persisted after therapy was discontinued. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

PRECAUTIONS: ***Information for Patients and Prescribers:*** **Females of childbearing potential should be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use effective contraception while taking Accutane and for 1 month after Accutane has been stopped. They should also sign a consent form prior to beginning Accutane therapy. They should be instructed to join the Accutane Survey and to review the patient videotape provided by Roche to the prescriber that provides information about contraception, the most common reasons that contraception fails, and the importance of using effective contraception when taking teratogenic drugs. Female patients should also be seen monthly and have a urine or serum pregnancy test performed each month during treatment to**

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confirm negative pregnancy status (see boxed CONTRAINDICATIONS AND WARNINGS).

- Patients should be informed that they must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events.

- Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane.

- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.

- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS: *Skin and Appendages*).

- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.

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

- Patients should be informed that approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted (see ADVERSE REACTIONS: *Musculoskeletal*).

- Neutropenia and rare cases of agranulocytosis have been reported. Accutane should be discontinued if clinically significant decreases in white cell counts occur.

Hypersensitivity: Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy and appropriate medical management.

Drug Interactions:

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

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- Concomitant treatment with Accutane and tetracyclines should be avoided because Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.

- Microdosed progesterone preparations (minipills) may be an inadequate method of contraception during Accutane therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, even when one of the forms is a hormonal contraceptive method (see boxed CONTRAINDICATIONS AND WARNINGS).

Laboratory Tests:

- *Pregnancy Test:* Female patients of childbearing potential must have negative results from two urine or serum pregnancy tests with a sensitivity of at least 50 mIU/mL before a prescription is given. The first test is to be performed at the office visit when the patient is qualified for Accutane therapy by her prescriber. The second test is to be performed on the second day of her next menstrual cycle or 11 days after her last unprotected act of sexual intercourse, whichever is later. Additional pregnancy tests are to be conducted monthly during treatment.

- *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, 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 Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see WARNINGS: *Lipids*).

- *Liver Function Tests:* Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS: *Hepatotoxicity*).

- *Glucose:* Some patients receiving Accutane have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane therapy, although no causal relationship has been established.

- *CPK:* Some patients undergoing vigorous physical activity while on Accutane therapy have experienced elevated CPK levels; however, the clinical significance is unknown.

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Carcinogenesis, Mutagenesis and Impairment of Fertility: In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (0.7 or 2.7 times the maximum clinical dose, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 × background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8 or 32 mg/kg/day (0.2, 0.7, or 2.7 times the maximum clinical dose, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (5 or 15 times the maximum clinical dose, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Accutane (isotretinoin) therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

Pregnancy: **Category X. See boxed CONTRAINDICATIONS AND WARNINGS.**

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Accutane.

ADVERSE REACTIONS: ***Clinical Trials and Postmarketing Surveillance:*** The adverse reactions listed below reflect the experience from investigational studies of Accutane, and the postmarketing experience. The relationship of some of these events to Accutane therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Accutane are similar to those described in patients taking very high

doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal passage, and eyes).

Dose Relationship: Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were reversible when therapy was discontinued; however, some persisted after cessation of therapy (see WARNINGS and ADVERSE REACTIONS).

Body as a Whole: allergic reactions, including vasculitis, systemic hypersensitivity (see PRECAUTIONS: *Hypersensitivity*), edema, fatigue, lymphadenopathy, weight loss

Cardiovascular: palpitation, tachycardia, vascular thrombotic disease, stroke

Endocrine/Metabolic: Hypertriglyceridemia (see WARNINGS: *Lipids*), alterations in blood sugar levels (see PRECAUTIONS: *Laboratory Tests*)

Gastrointestinal: inflammatory bowel disease (see WARNINGS: *Inflammatory Bowel Disease*), hepatitis (see WARNINGS: *Hepatotoxicity*), pancreatitis (see WARNINGS: *Lipids*), bleeding and inflammation of the gums, colitis, ileitis, nausea, other nonspecific gastrointestinal symptoms

Hematologic: allergic reactions (see PRECAUTIONS: *Hypersensitivity*), anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis (see PRECAUTIONS: *Information for Patients and Prescribers*). See PRECAUTIONS: *Laboratory* for other hematological parameters.

Musculoskeletal: skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure (see WARNINGS: *Skeletal*), mild to moderate musculoskeletal symptoms including arthralgia (see PRECAUTIONS: *Information for Patients and Prescribers*), transient pain in the chest (see PRECAUTIONS: *Information for Patients and Prescribers*), elevations of CPK (see PRECAUTIONS: *Laboratory Tests*), arthritis, tendonitis, other types of bone abnormalities

Neurological: pseudotumor cerebri (see WARNINGS: *Pseudotumor Cerebri*), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness

Psychiatric: suicidal ideation, suicide attempts, suicide, depression, psychosis (see WARNINGS: *Psychiatric Disorders*), emotional instability

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.

Reproductive System: abnormal menses

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Respiratory: bronchospasms (with or without a history of asthma), respiratory infection, voice alteration

Skin and Appendages: acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas[7], flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, sweating, urticaria, vasculitis (including Wegener's granulomastosis; see PRECAUTIONS: *Hypersensitivity*), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see PRECAUTIONS: *Information for Patients and Prescribers*)

Special Senses: Hearing: Hearing impairment (see WARNINGS: *Hearing Impairment*), tinnitus. *Vision:* corneal opacities (see WARNINGS: *Corneal Opacities*), decreased night vision which may persist (see WARNINGS: *Decreased Night Vision*), cataracts, color vision disorder, conjunctivitis, dry eyes, eye lid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

Urinary System: glomerulonephritis (see PRECAUTIONS: *Hypersensitivity*), nonspecific urogenital findings (see PRECAUTIONS: *Laboratory* for other urological parameters)

Laboratory: Elevation of plasma triglycerides (see WARNINGS: *Lipids*), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment

Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see WARNINGS: *Hepatotoxicity*)

Elevation of fasting blood sugar, elevations of CPK (see PRECAUTIONS: *Laboratory Tests*), hyperuricemia

Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis; see PRECAUTIONS: *Information for Patients and Prescribers*), elevated sedimentation rates, elevated platelet counts, thrombocytopenia

White cells in the urine, proteinuria, microscopic or gross hematuria

OVERDOSAGE: The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice (>300 times the maximum clinical dose after normalization of the rat dose for total body surface area and >150 times the maximum clinical dose after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (327 times the maximum clinical dose after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis,

abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without apparent residual effects.

DOSAGE AND ADMINISTRATION: The recommended dosage range for Accutane is 0.5 to 2 mg/kg given in 2 divided doses daily for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages.

It is recommended that for most patients the initial dosage of Accutane be 0.5 to 1 mg/kg/day. Patients whose disease is very severe or is primarily manifested on the trunk may require up to the maximum recommended dosage, 2 mg/kg/day. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see WARNINGS: *Skeletal: Hyperostosis* and *Premature Epiphyseal Closure*).

Contraceptive measures must be followed for any subsequent course of therapy (see boxed CONTRAINDICATIONS AND WARNINGS).

Accutane should be administered with food.

ACCUTANE DOSING BY BODY WEIGHT

Body Weight		Total Mg/Day		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

HOW SUPPLIED: Soft gelatin capsules, 10 mg (light pink), imprinted ACCUTANE 10 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0155-49).

Soft gelatin capsules, 20 mg (maroon), imprinted ACCUTANE 20 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0169-49).

ACCUTANE® (isotretinoin)

Soft gelatin capsules, 40 mg (yellow), imprinted ACCUTANE 40 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0156-49).

Store at controlled room temperature (59° to 86°F, 15° to 30°C). Protect from light.

REFERENCES:

1. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remissions of cystic and conglobate acne with 13-*cis*-retinoic acid. *N Engl J Med* 300:329-333, 1979. 2. Pochi PE, Shalita AR, Strauss JS, Webster SB. Report of the consensus conference on acne classification. *J Am Acad Dermatol* 24:495-500, 1991. 3. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-*cis*-retinoic acid: evaluation of sebum production and the clinical response in a multiple-dose trial. *J Am Acad Dermatol* 3:602-611, 1980. 4. Jones H, Blanc D, Cunliffe WJ. 13-*cis*-retinoic acid and acne. *Lancet* 2:1048-1049, 1980. 5. Katz RA, Jorgensen H, Nigra TP. Elevation of serum triglyceride levels from oral isotretinoin in disorders of keratinization. *Arch Dermatol* 116:1369-1372, 1980. 6. Ellis CN, Madison KC, Pennes DR, Martel W, Voorhees JJ. Isotretinoin therapy is associated with early skeletal radiographic changes. *J Am Acad Dermatol* 10:1024-1029, 1984. 7. Dicken CH, Connolly SM. Eruptive xanthomas associated with isotretinoin (13-*cis*-retinoic acid). *Arch Dermatol* 116:951-952, 1980. 8. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol* 10:490-496, 1984.

PATIENT CONSENT FORM

To be completed by the patient, her parent/guardian*
and signed by her prescriber.

Please read each item below and initial in the space provided to indicate that you understand each item and agree to follow your prescriber's instructions. **DO NOT SIGN THIS CONSENT AND DO NOT TAKE ACCUTANE IF THERE IS ANYTHING THAT YOU DO NOT UNDERSTAND.** A parent or guardian of a minor patient must also read and understand each item before signing the consent.

1. I, _____,
(Patient's Name)
understand that Accutane is a very powerful medicine with the potential for serious Adverse Effects that is used to treat severe nodular acne that did not get better with other treatments including oral antibiotics.

Initials: _____

ACCUTANE® (isotretinoin)

2. I understand that I must not take Accutane (isotretinoin) if I am pregnant. I understand that I must not take Accutane if I am able to become pregnant and I am not using the required two separate forms of effective methods of birth control.

   Initials: _____

3. I understand from my prescriber that although not every fetus exposed to Accutane has resulted in a deformed child, there is an extremely high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected.

   Initials: _____

4. I understand that I must avoid pregnancy during the entire time of my treatment and for 1 month after the end of my treatment with Accutane.

   Initials: _____

5. I understand that if I am able to become pregnant and unless I absolutely and consistently abstain from sexual intercourse, I must use two separate, effective forms of birth control (contraception) **AT THE SAME TIME.**

   Initials: _____

6. I understand from discussions with my prescriber that birth control pills and injectable/implantable birth control products are the most effective forms of birth control. I understand that there have been reports of pregnancy from women who have used birth control pills, as well as women who have used injectable/implantable birth control products and I understand that pregnancies occur more often when only a single method of birth control is used. Therefore, I understand that it is essential that I use two different methods, even if one of the methods I choose is birth control pills or injectable/implantable birth control products.

   Initials: _____

7. I understand that the following are considered effective forms of contraception:
   Primary: Tubal ligation, partner's vasectomy, birth control pills, injectable/implantable birth control products, and an IUD
   Secondary: Diaphragms, latex condoms, and cervical caps; each must be used with a spermicide.

   I understand that at least one of my two chosen methods of birth control must be a primary method, and that any birth control method can fail, even when two forms are used at the same time.

   Initials: _____

ACCUTANE® (isotretinoin)

8. I understand that I may receive free initial contraceptive counseling and pregnancy testing from a consulting physician or family planning center. I understand that my Accutane prescriber can provide me with an Accutane Patient Referral Form for this consultation.

   Initials: _____

9. I understand that I must begin actively avoiding pregnancy as described above at least 1 month before taking the first dose of Accutane, throughout treatment with Accutane and for 1 month after I have completed Accutane treatment.

   Initials: _____

10. I understand that I cannot receive a prescription for Accutane unless I have 2 negative pregnancy test results. The first pregnancy test should be during the office visit when my prescriber decides to prescribe Accutane. The second test should be on the second day of my next menstrual cycle or 11 days after the last time I had unprotected sexual intercourse, whichever is later. I understand that I will have additional pregnancy testing, monthly, throughout my Accutane therapy.

    Initials: _____

11. I understand that I should not start Accutane until I am sure that I am not pregnant and have negative results from 2 pregnancy tests.

    Initials: _____

12. I have read and understand the materials my prescriber has given to me, including the brochure *Important Information Concerning Your Treatment with Accutane® (isotretinoin).* I have watched and understand the Roche video provided to me by my prescriber about contraception. I have also been told about a confidential counseling line that I may call for additional information about birth control and I have received information on emergency contraception.

    Initials: _____

13. I understand that I must not share my medication with anyone else and that I should not give blood until 1 month after taking my last dose of Accutane, because if I do, someone else's unborn baby may be exposed to Accutane.

    Initials: _____

14. I understand that I must immediately stop taking Accutane and inform my prescriber if I become pregnant, miss my menstrual period, or stop using birth control.

    Initials: _____

ACCUTANE® (isotretinoin)

15. I have been given information about the confidential Accutane Survey by my prescriber and he/she has explained to me how important it is to join the Accutane Survey.

    Initials: _____

My prescriber has answered all my questions about Accutane and the Accutane information provided to me. I understand all the information I have received and that avoiding pregnancy during Accutane treatment is my responsibility.

Initials: _____

I now authorize my prescriber _____ to begin my treatment with Accutane.

Patient signature:_____ Date:_____

Parent/guardian signature:_____ Date:_____

Please print: Patient name and address_____

_____ Telephone (area code)_____

I have fully explained to the patient, _____, the nature and purpose of the treatment described above and the risks to females of childbearing potential. I have asked the patient if she has any questions regarding her treatment with Accutane and have answered those questions to the best of my ability.

Prescriber signature: _____ Date:_____

*if patient is a minor under the age of 18.

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27897043-0400

ACCUTANE® (isotretinoin)

Revised: April 2000
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-038

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

OCT 31 1999

Medical Officer Review
Labeling Changes being Effected: Contraception

NDA#: **18-662**

HFD 540#: 994169
Doc ID#: SLR-038

Stamp Date: September 13, 1999
Date Received: October 13, 1999
Review Date: October 15, 1999

Sponsor: Hoffman-La Roche

Product: Accutane (isotretinoin)

Indication: Severe recalcitrant nodular acne

Formulation: Capsule

Summary: This submission is a CBE for labeling regarding contraceptive drug failure (this issue has been previously reviewed). The submitted labeling changes to the black box Warning regarding contraceptive failure are identical to the wording agreed upon in meetings with the Sponsor. In addition, the Sponsor has changed 4 items in the Informed Consent checklist to address the contraceptive failure issue. These changes are consistent with the agreed upon Warning wording, and also serve to describe more fully the measures available to patients to prevent fetal exposure.

[redacted]

when two forms are used simultaneously." I would recommend that this sentence state "*I understand that at least one of the two methods I choose should be a primary birth control method,* and that any birth control method can fail, even when two forms are used simultaneously". For example, a patient whose partner has had a vasectomy may choose to use oral contraceptives.

The submission also includes a detailed administrative timeline for implementation of this labeling change, as well as the upcoming adverse event and Pregnancy Prevention Program changes. This administrative timetable is attached for reference. Note that the changes in this submission (contraceptive failure) are slated for implementation in December 1999 if promotional materials have been approved by DDMAC. The Sponsor proposes to include this labeling revision in a Dear Doctor letter to be sent when all of the safety issues in the

labeling have been addressed, a goal they would like to reach in time for the American Academy of Dermatology meeting in March 2000.

Recommendation:

1) Fax the following suggestion to Sponsor for Item #7 of the Informed Consent: change the last sentence from "I understand that I should use one primary and one secondary birth control method, and that any birth control method can fail, even when two forms are used simultaneously" to *"I understand that at least one of the two methods I choose should be a primary birth control method, and that any birth control method can fail, even when two forms are used simultaneously"*. The rationale is that a patient may wish to use two methods considered primary, for example, a patient whose partner has had a vasectomy may choose to use oral contraceptives.

2) Schedule an internal meeting to discuss administrative issues regarding implementation and review resources.

Kathryn O'Connell MD 10/19/99

Kathryn O'Connell, MD

cc: NDA 18-662

HFD-540
HFD-540/PM/White
HFD-540/Pharm/Nostrandt
HFD-540/Chem/Timmer
HFD-540/MO/OConnell
HFD-540/TL/Walker
HFD-540/DD/Wilkin

SW 10/25/99

10/31/99