CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-662 / S-054

Trade Name: Accutane

Generic Name: (isotretinoin)

Sponsor: Hoffman La Roche Inc.

Approval Date: August 24, 2004

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-054

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-662 S/054

Hoffman-La Roche, Inc.
Attention: Ellen Carey, Pharm.D.
Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Carey:

Please refer to your supplemental new drug application dated February 20, 2004, received February 24, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) Capsules, 10 mg, 20 mg and 40 mg.

This supplemental new drug application provides for the following labeling revisions:

1. Black Box CONTRAINDICATIONS and WARNINGS: Addition of "(see PRECAUTIONS: Drug Interactions)" following "A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane".
2. PRECAUTIONS: Drug Interactions: Addition of the following bullet: *Norethindrone/ethinyl estradiol:* In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent, Accutane at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
3. Addition of the statement "OrthoNovum 7/7/7 is a registered trademark of Ortho-McNeil Pharmaceutical, Inc." at the end of the package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the Package Insert, text for the Patient Information/Consent (for female patients concerning birth defects), Informed Consent/Patient Agreement (for all patients), and the text for the Medication Guide).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 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-054". Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}
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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
8/24/04 06:41:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-054

APPROVED LABELING

Roche

ACCUTANE®

(isotretinoin)

CAPSULES

R_x only

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

Accutane must not be used by females who are pregnant. 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.

Major human fetal abnormalities related to Accutane administration in females have been documented. There is an increased risk of spontaneous abortion. In addition, premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; 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.

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

- **<u>Must</u> NOT be pregnant or breast feeding.**

- **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 be reliable in understanding and carrying out instructions.**

Accutane must be prescribed under the *System to Manage Accutane Related Teratogenicity™* (S.M.A.R.T.™).

To prescribe Accutane, the prescriber must obtain a supply of yellow self-adhesive Accutane Qualification Stickers. To obtain these stickers:

1) **Read the booklet entitled *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) *Guide to Best Practices*.**
2) **Sign and return the completed S.M.A.R.T. *Letter of Understanding* containing the following Prescriber Checklist:**

- **I know the risk and severity of fetal injury/birth defects from Accutane**
- **I know how to diagnose and treat the various presentations of acne**
- **I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy**
- **It is the informed patient's responsibility to avoid pregnancy during Accutane therapy and for 1 month after stopping Accutane. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Accutane I will refer for expert, detailed pregnancy prevention counseling and prescribing, reimbursed by the manufacturer, OR I have the expertise to perform this function and elect to do so**
- **I understand, and will properly use throughout the Accutane treatment course, the S.M.A.R.T. procedures for Accutane, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Accutane Qualification Stickers**

3) **To use the yellow self-adhesive Accutane Qualification Sticker: Accutane should not be prescribed or dispensed to any patient (male or female) without a yellow self-adhesive Accutane Qualification Sticker.**

For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies that she:

- **Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated every month prior to the female patient receiving each prescription.**
- **Must have selected and have committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month after discontinuing Accutane therapy. Counseling about**

contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/implantable/insertable hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception simultaneously. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane (See PRECAUTIONS: Drug Interactions). Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. These reports occurred while these patients were taking Accutane. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- **Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.**
- **Must have been informed of the purpose and importance of participating in the Accutane Survey and have been given the opportunity to enroll (see PRECAUTIONS).**

The yellow self-adhesive Accutane Qualification Sticker documents that the female patient is qualified, and includes the date of qualification, patient gender, cut-off date for filling the prescription, and up to a 30-day supply limit with no refills.

These yellow self-adhesive Accutane Qualification Stickers should also be used for male patients.

Table 1. Use of Pregnancy Tests and Accutane Qualification Stickers for Patients

Patient Type	Pregnancy Test Required	Qualification Date	Accutane Qualification Sticker Necessary	Dispense Within 7 Days of Qualification Date
All Males	No	Date Prescription Written	Yes	Yes
Females of Childbearing Potential	Yes	Date Sample Taken for Confirmatory Negative Pregnancy Test	Yes	Yes
Females* Not of Childbearing	No	Date Prescription Written	Yes	Yes

Potential				
*Females who have had a hysterectomy or who are postmenopausal are not considered to be of childbearing potential.				

If a pregnancy does occur during treatment of a woman with Accutane, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to Roche @ 1-800-526-6367 where a Roche Pregnancy Prevention Program Specialist will be available to discuss Roche pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

Accutane should be prescribed only by prescribers who have demonstrated special competence in the diagnosis and treatment of severe recalcitrant nodular acne, are experienced in the use of systemic retinoids, have read the S.M.A.R.T. *Guide to Best Practices,* signed and returned the *completed* S.M.A.R.T. *Letter of Understanding*, and obtained yellow self-adhesive Accutane Qualification Stickers. Accutane should not be prescribed or dispensed without a yellow self-adhesive Accutane Qualification Sticker.

INFORMATION FOR PHARMACISTS:

ACCUTANE MUST ONLY BE DISPENSED:

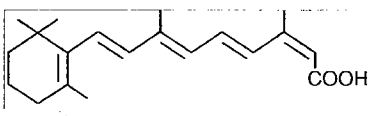
- **IN NO MORE THAN A 30-DAY SUPPLY**
- **ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **WITHIN 7 DAYS OF THE QUALIFICATION DATE**
- **REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **NO TELEPHONE OR COMPUTERIZED PRESCRIPTIONS ARE PERMITTED.**

AN ACCUTANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME ACCUTANE IS DISPENSED, AS REQUIRED BY LAW. THIS ACCUTANE MEDICATION GUIDE IS AN IMPORTANT PART OF THE RISK MANAGEMENT PROGRAM FOR THE PATIENT.

DESCRIPTION

Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and 40-mg soft gelatin capsules for oral administration. Each capsule 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 to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



CLINICAL PHARMACOLOGY

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1.0 mg/kg/day (see DOSAGE AND ADMINISTRATION), inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin 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

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. In a crossover study, 74 healthy adult subjects received a single 80 mg oral dose (2 x 40 mg capsules) of Accutane under fasted and fed conditions. Both peak plasma concentration (C_{max}) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with Accutane given under fasted conditions (see Table 2 below). The observed elimination half-life was unchanged. This lack of change in half-life suggests that food increases the bioavailability of isotretinoin without altering its disposition. The time to peak concentration (T_{max}) was also increased with food and may be related to a longer absorption phase. Therefore, Accutane capsules should always be taken with food (see DOSAGE AND ADMINISTRATION). Clinical studies have shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

Table 2. Pharmacokinetic Parameters of Isotretinoin Mean (%CV), N=74

Accutane 2 x 40 mg Capsules	$AUC_{0-\infty}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Fed*	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

*Eating a standardized high-fat meal

Distribution

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

Metabolism

Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-*oxo*-isotretinoin, retinoic acid (tretinoin), and 4-*oxo*-retinoic acid (4-*oxo*-tretinoin). Retinoic acid and 13-*cis*-retinoic acid are geometric isomers and show reversible interconversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-tretinoin.

After a single 80 mg oral dose of Accutane to 74 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.

All of these metabolites possess retinoid activity that is in some in vitro models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (≥18 years), the exposure of patients to 4-*oxo*-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

Elimination

Following oral administration of an 80 mg dose of ^{14}C-isotretinoin as a liquid suspension, ^{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%). After a single 80 mg oral dose of Accutane to 74 healthy adult subjects under fed conditions, the mean ± SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin were 21.0 ± 8.2 hours and 24.0 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43 in patients with cystic acne.

Special Patient Populations

Pediatric Patients

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (≥18 years) who received Accutane for the treatment of severe recalcitrant nodular acne. In both age groups, 4-*oxo*-isotretinoin was the major metabolite; tretinoin and 4-*oxo*-tretinoin were also observed. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in Table 3 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

Table 3. Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12 to 15 Years of Age
Mean (± SD), N=38*

Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
C_{max} (ng/mL)	573.25 (278.79)	731.98 (361.86)
$AUC_{(0-12)}$ (ng·hr/mL)	3033.37 (1394.17)	5082.00 (2184.23)
$AUC_{(0-24)}$ (ng·hr/mL)	6003.81 (2885.67)	–
T_{max} (hr)†	6.00 (1.00-24.60)	4.00 (0-12.00)
Css_{min} (ng/mL)	–	352.32 (184.44)
$T_{1/2}$ (hr)	–	15.69 (5.12)
CL/F (L/hr)	–	17.96 (6.27)

*The single and multiple dose data in this table were obtained following a non-standardized meal that is not comparable to the high-fat meal that was used in the study in Table 2.
†Median (range)

In pediatric patients (12 to 15 years), the mean ± SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin were 15.7 ± 5.1 hours and 23.1 ± 5.7 hours, respectively. The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 for pediatric patients.

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, Accutane is indicated only for those females who are not pregnant, because Accutane can cause severe birth defects (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: Bone Mineral Density, 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, suicide, and aggressive and/or violent behaviors. 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). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane® (isotretinoin).*

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.

Lipids

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with Accutane. Marked elevations of serum triglycerides 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 (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day 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 (30 to 60 times the recommended clinical dose of 1.0 mg/kg/day, 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 for 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

Bone Mineral Density

Effects of multiple courses of Accutane on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range –1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see PRECAUTIONS: Pediatric Use).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the Accutane population. While causality to Accutane has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Accutane be given at the recommended doses for no longer than the recommended duration.

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.

In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of Accutane given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Premature Epiphyseal Closure

There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Accutane. The effect of multiple courses of Accutane on epiphyseal closure is 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

The Accutane Pregnancy Prevention and Risk Management Programs consist of the *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) and the Accutane Pregnancy Prevention Program (PPP). S.M.A.R.T. should be followed for prescribing Accutane with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) reading the booklet entitled *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) *Guide to Best Practices*, 2) signing and returning the completed S.M.A.R.T. *Letter of Understanding* containing the Prescriber Checklist, 3) a yellow self-adhesive Accutane Qualification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Be Smart, Be Safe, Be Sure*, should be used with each patient.

The following further describes each component:

1) The S.M.A.R.T. *Guide to Best Practices* includes: Accutane teratogenic potential, information on pregnancy testing, specific information about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy, the methods to evaluate pregnancy risk, and the method to complete a qualified Accutane prescription.
2) The S.M.A.R.T. *Letter of Understanding* attests that Accutane prescribers understand that Accutane is a teratogen, have read the S.M.A.R.T. *Guide to Best Practices,* understand their responsibilities in preventing exposure of pregnant females to Accutane and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.

   The Prescriber Checklist attests that Accutane prescribers know the risk and severity of injury/birth defects from Accutane; know how to diagnose and treat the various presentations of acne; know the risk factors for unplanned pregnancy and the effective measures for avoidance; will refer the patient for, or provide, detailed pregnancy prevention counseling to help the patient have knowledge and tools needed to fulfill their ultimate responsibility to avoid becoming pregnant; understand and properly use throughout the Accutane treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and use of qualified prescriptions with the yellow self-adhesive Accutane Qualification Sticker.

3) The yellow self-adhesive Accutane Qualification Sticker is used as documentation that the prescriber has qualified the female patient according to the qualification criteria (see boxed CONTRAINDICATIONS AND WARNINGS).
4) Accutane Pregnancy Prevention Program (PPP) is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The PPP includes information on the risks and benefits of Accutane which is linked to the Accutane Medication Guide dispensed by pharmacists with each prescription.

   Male and female patients are provided with separate booklets. Each booklet contains information on Accutane therapy, including precautions and warnings, an Informed Consent/Patient Agreement form, and a toll-free line which provides Accutane information in 13 languages.

   The booklet for male patients, *Be Smart, Be Safe, Be Sure, Accutane Risk Management Program for Men,* also includes information about male reproduction, a warning not to share Accutane with others or to donate blood during Accutane therapy and for 1 month following discontinuation of Accutane.

   The booklet for female patients, *Be Smart, Be Safe, Be Sure, Accutane Pregnancy Prevention and Risk Management Program for Women,* also includes a referral program that offers females free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; a second Patient Information/Consent form concerning birth defects, obtaining her consent to be treated within this agreement; an enrollment form for the Accutane Survey; and a qualification checklist affirming the conditions under which female patients may receive Accutane. In addition, there is information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, and the rates of possible contraceptive failure; a toll-free contraception counseling line; and patient education videos — the video "Be Prepared, Be Protected" and the video "Be Aware: The Risk of Pregnancy While on Accutane".

General

Although an effect of Accutane on bone loss is not established, physicians should use caution when prescribing Accutane to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on treatment with Accutane or following cessation of treatment with Accutane while involved in these activities. While causality to Accutane has not been established, an effect cannot be ruled out.

Information for Patients and Prescribers

- Patients should be instructed to read the Medication Guide supplied as required by law when Accutane is dispensed. The complete text of the Medication Guide is reprinted at the end of this document. For additional information, patients should also read the *Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin).* All patients should sign the Informed Consent/Patient Agreement.
- Females of childbearing potential should be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Accutane, 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 given an opportunity to enroll in the Accutane Survey and to review the patient videotapes provided by the manufacturer to the prescriber. The videos include information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a woman who is pregnant takes Accutane at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).
- Accutane is found in the semen of male patients taking Accutane, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.
- Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether or not Accutane therapy is appropriate in this setting (see WARNINGS: Psychiatric Disorders).
- 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 reminded to take Accutane with a meal (see DOSAGE AND ADMINISTRATION). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.
- 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). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see Laboratory Tests: CPK).
- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female than male patients. Arthralgias were experienced in 22% (79/358) of pediatric-patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane. Consideration should be given to discontinuation of Accutane if any significant abnormality is found.
- 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

- *Vitamin A:* 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.
- *Tetracyclines:* 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.
- *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) 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 combined oral contraceptives, as well as

topical/injectable/implantable/insertable hormonal birth control 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 for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see boxed CONTRAINDICATIONS AND WARNINGS).

- *Norethindrone/ethinyl estradiol:* In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent, Accutane at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- *Phenytoin:* Accutane has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane. Therefore, caution should be exercised when using these drugs together.
- *Systemic Corticosteroids*: Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane. Therefore, caution should be exercised when using these drugs together.

Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. **Accutane use is associated with depression in some patients (see WARNINGS: Psychiatric Disorders and ADVERSE REACTIONS: Psychiatric).** Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

Laboratory Tests

Pregnancy Test

Female patients of childbearing potential must have negative results from 2 urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane (a screening test). The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception).

Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month prior to the female patient receiving each prescription.

- *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. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

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 (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day, 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 x 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 (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0 mg/kg/day, 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 (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day, 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.

Pediatric Use

The use of Accutane in pediatric patients less than 12 years of age has not been studied. The use of Accutane for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see PRECAUTIONS: General). Use of Accutane in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (≥18 years). Results from this study demonstrated that Accutane, at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

In studies with Accutane, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see ADVERSE REACTIONS).

In an open-label clinical trial (N=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range –1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see WARNINGS: Skeletal: Bone Mineral Density).

Geriatric Use

Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see WARNINGS and PRECAUTIONS).

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, esophagitis/esophageal ulceration, 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 Tests for other hematological parameters.

Musculoskeletal

skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density (see WARNINGS: Skeletal), musculoskeletal symptoms (sometimes severe) including back pain and arthralgia (see PRECAUTIONS: Information for Patients and Prescribers), transient pain in the chest (see PRECAUTIONS: Information for Patients and Prescribers), arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis (see PRECAUTIONS: Laboratory Tests).

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, aggression, violent behaviors (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

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 granulomatosis; 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, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

Urinary System

glomerulonephritis (see PRECAUTIONS: Hypersensitivity), nonspecific urogenital findings (see PRECAUTIONS: Laboratory Tests 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 (>600 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the rat dose for total body surface area and >300 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1.0 mg/kg/day 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.

Accutane causes serious birth defects at any dosage (see boxed CONTRAINDICATIONS AND WARNINGS). Females of childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the boxed CONTRAINDICATIONS AND WARNINGS. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in the boxed CONTRAINDICATIONS AND WARNINGS. Educational materials for such patients can be obtained by calling the manufacturer. Because an overdose would be expected to result in higher levels of isotretinoin in semen than found during a normal treatment course, male patients should use a condom, or avoid reproductive sexual activity with a female who is or might become pregnant, for 30 days after the overdose. All patients with isotretinoin overdose should not donate blood for at least 30 days.

DOSAGE AND ADMINISTRATION

Accutane should be administered with a meal (see PRECAUTIONS: Information for Patients and Prescribers).

The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 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. 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. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

The safety of once daily dosing with Accutane has not been established. Once daily dosing is **not** recommended.

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. Long-term use of Accutane, even in low doses, has not been studied, and is not recommended. It is important that Accutane be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Accutane on bone loss is unknown (see WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure).

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

Table 4. Accutane Dosing by Body Weight (Based on Administration With Food)

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

*See DOSAGE AND ADMINISTRATION: the recommended dosage range is 0.5 to 1.0 mg/kg/day.

Information for Pharmacists

Accutane must only be dispensed in no more than a 30-day supply and only on presentation of an Accutane prescription with a yellow self-adhesive Accutane Qualification Sticker within 7 days of the qualification date. **REFILLS REQUIRE A NEW WRITTEN PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER WITHIN 7 DAYS OF THE QUALIFICATION DATE.** No telephone or computerized prescriptions are permitted.

An Accutane Medication Guide must be given to the patient each time Accutane is dispensed, as required by law. This Accutane Medication Guide is an important part of the risk management program for the patient.

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).

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

Storage

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

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Revised: August 2004

PATIENT INFORMATION/CONSENT (for female patients concerning birth defects)

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

Read each item below and initial in the space provided to show 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 (under age 18) must also read and initial each item before signing the consent.

_____
(Patient's Name)

1. I understand that there is a very 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. This is why I must not be pregnant while taking Accutane.

   Initial: _____

2. I understand that I must not take Accutane (isotretinoin) if I am pregnant.

   Initial: _____

3. I understand that I must not get pregnant during the entire time of my treatment and for 1 month after the end of my treatment with Accutane.

   Initial: _____

4. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) **at the same time**. The only exception is if I have had surgery to remove the womb (a hysterectomy).

   Initial: _____

5. I understand that birth control pills and topical/injectable/implantable/insertable hormonal birth control products are among the most effective forms of birth control. However, any form of birth control can fail. Therefore, I must use 2 different methods at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is birth control pills or topical/injectable/implantable/insertable hormonal birth control.

   Initial: _____

6. I will talk with my prescriber about any drugs or herbal products I plan to take during my Accutane treatment because hormonal birth control methods (for example, birth control pills) may not work if I am taking certain drugs or herbal products (for example, St. John's Wort).

Initial: _____

7. I understand that the following are considered effective forms of birth control:

   Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills, topical/injectable/implantable/insertable hormonal birth control products, and an IUD (intrauterine device).
   Secondary: Diaphragms, latex condoms, and cervical caps. Each must be used with a spermicide, which is a special cream or jelly that kills sperm.

   I understand that at least 1 of my 2 methods of birth control must be a primary method.

   Initial: _____

8. I understand that I may receive a free contraceptive (birth control) counseling session from a doctor or other family planning expert. My Accutane prescriber can give me an Accutane Patient Referral Form for this free consultation.

   Initial: _____

9. I understand that I must begin using the birth control methods I have chosen as described above at least 1 month before I start taking Accutane.

   Initial: _____

10. I understand that I cannot get a prescription for Accutane unless I have 2 negative pregnancy test results. The first pregnancy test should be done when my prescriber decides to prescribe Accutane. The second pregnancy test should be done during the first 5 days of my menstrual period right before starting Accutane therapy, or as instructed by my prescriber. I will then have 1 pregnancy test every month during my Accutane therapy.

    Initial: _____

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

    Initial: _____

12. I have read and understand the materials my prescriber has given to me, including the *Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin)*. My prescriber gave me and asked me to watch the videos about contraception. I was told about a confidential counseling line that I may call for more information about birth control. I have received information on emergency contraception (birth control).

    Initial: _____

13. I understand that I must stop taking Accutane right away and inform my prescriber if I get pregnant, miss my menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods at any time.

Initial: _____

14. My prescriber gave me information about the confidential Accutane Survey and explained to me how important it is to take part in the Accutane Survey.

Initial: _____

15. I understand that the yellow self-adhesive Accutane Qualification Sticker on my prescription for Accutane means that I am qualified to receive an Accutane prescription, because I:

- have had 2 negative urine or serum pregnancy tests before receiving the initial Accutane prescription. I must have a negative result from a urine or serum pregnancy test repeated each month prior to my receiving each subsequent prescription.

- have selected and committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or I have undergone a hysterectomy. I must use 2 forms of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. I must receive counseling, repeated on a monthly basis, about contraception and behaviors associated with an increased risk of pregnancy.

- have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.

- have been informed of the purpose and importance of participating in the Accutane Survey and given the opportunity to enroll.

Initial: _____

My prescriber has answered all my questions about Accutane and I understand that <u>it is my responsibility not to get pregnant</u> during Accutane treatment <u>or for 1 month after I stop taking Accutane</u>.

Initial: _____

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

Patient Signature:_____ Date:_____

Parent/Guardian Signature (if under age 18):_____ Date:_____

Please print: Patient Name and Address_____
_____ Telephone _____

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:_____

INFORMED CONSENT/PATIENT AGREEMENT (for all patients):

To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber.

Read each item below and initial in the space provided if you understand each item and agree to follow your prescriber's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.

Do not sign this agreement and do not take Accutane if there is anything that you do not understand about all the information you have received about using Accutane.

1. I, _____,
   (Patient's Name)
   understand that Accutane is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.

   Initials: _____

2. My prescriber has told me about my choices for treating my acne.

   Initials: _____

3. I understand that there are serious side effects that may happen while I am taking Accutane. These have been explained to me. These side effects include serious birth defects in babies of pregnant females. (Note: There is a second Informed Consent form for female patients concerning birth defects.)

   Initials: _____

4. I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane. Some people have had other signs of depression while taking Accutane (see #7 below).

   Initials: _____

5. Before I start taking Accutane, I agree to tell my prescriber if, to the best of my knowledge, I have **ever** had symptoms of depression (see #7 below), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

Initials: _____

6. Before I start taking Accutane, I agree to tell my prescriber if, to the best of my knowledge, anyone in my family has ever had symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.

   Initials: _____

7. Once I start taking Accutane, I agree to stop using Accutane and tell my prescriber right away if any of the following happen. I:

- Start to feel sad or have crying spells
- Lose interest in activities I once enjoyed
- Sleep too much or have trouble sleeping
- Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- Have a change in my appetite or body weight
- Have trouble concentrating
- Withdraw from my friends or family
- Feel like I have no energy
- Have feelings of worthlessness or inappropriate guilt
- Start having thoughts about hurting myself or taking my own life (suicidal thoughts)

   Initials: _____

8. **I agree to return to see my prescriber every month I take Accutane to get a new prescription for Accutane, to check my progress, and to check for signs of side effects.**

   Initials: _____

9. Accutane will be prescribed just for me—I will not share Accutane with other people because it may cause serious side effects, including birth defects.

   Initials: _____

10. I will not give blood while taking Accutane or for 1 month after I stop taking Accutane. I understand that if someone who is pregnant gets my donated blood, her baby may be exposed to Accutane and may be born with serious birth defects.

    Initials: _____

11. I have read the *Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin),* and other materials my provider gave me containing important safety information about Accutane. I understand all the information I received.

    Initials: _____

12. My prescriber and I have decided I should take Accutane. I understand that each of my Accutane prescriptions must have a yellow self-adhesive Accutane Qualification Sticker on it. I understand that I can stop taking Accutane at any time. I agree to tell my prescriber if I stop taking Accutane.

Initials: _____

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

Patient Signature: _____ Date: _____

Parent/Guardian Signature (if under age 18): _____ Date: _____

Patient Name (print) _____

Patient Address _____ Telephone (___.___.___)

_____

I have:

- fully explained to the patient, _____, the nature and purpose of Accutane treatment, including its benefits and risks
- given the patient the appropriate educational materials, *Be Smart, Be Safe, Be Sure*, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane
- answered those questions to the best of my ability
- placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.

Prescriber Signature: _____ Date:_____

MEDICATION GUIDE

Read this Medication Guide every time you get a prescription or a refill for Accutane (ACK-u-tane). There may be new information. This information does not take the place of talking with your prescriber (doctor or other health care provider).

What is the most important information I should know about Accutane?

Accutane is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics. However, Accutane can cause serious side effects. Before starting Accutane, discuss with your prescriber how bad your acne is, the possible benefits of Accutane, and its possible side effects, to decide if Accutane is right for you. Your prescriber will ask you to read and sign a form or forms indicating you understand some of the serious risks of Accutane.

Possible serious side effects of taking Accutane include *birth defects* and *mental disorders.*

1. **Birth defects. Accutane can cause birth defects (deformed babies) if taken by a pregnant woman.** It can also cause miscarriage (losing the baby before birth), premature (early) birth, or death of the baby. Do not take Accutane if you are pregnant or plan to become pregnant while you are taking Accutane. Do not get pregnant for 1 month after you stop taking Accutane. Also, if you get pregnant while taking Accutane, stop taking it right away and call your prescriber.

   All females should read the section in this Medication Guide "What are the important warnings for females taking Accutane?"

2. **Mental problems and suicide.** Some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane.

   All patients should read the section in this Medication Guide "What are the signs of mental problems?"

   For other possible serious side effects of Accutane, see "What are the possible side effects of Accutane?" in this Medication Guide.

What are the important warnings for females taking Accutane?

You must not become pregnant while taking Accutane, or for 1 month after you stop taking Accutane. Accutane can cause severe birth defects in babies of women who take it while they are pregnant, even if they take Accutane for only a short time. **There is an extremely high risk that your baby will be deformed or will die** if you are pregnant while taking Accutane. Taking Accutane also increases the chance of miscarriage and premature births.

Female patients will not get their first prescription for Accutane unless there is proof they have had 2 negative pregnancy tests. The first test must be done when your prescriber decides to prescribe Accutane. The second pregnancy test must be done during the first 5 days of the menstrual period right before starting Accutane therapy, or as instructed by your prescriber. Each month of treatment, you must have a negative result from a urine or serum pregnancy test. Female patients cannot get another prescription for Accutane unless there is proof that they have had a negative pregnancy test.

A yellow self-adhesive Accutane Qualification Sticker on your prescription indicates to the pharmacist that you are qualified by your prescriber to get Accutane.

While you are taking Accutane, you **must** use effective birth control. **You must use 2 separate effective forms of birth control at the same time** for at least 1 month before starting Accutane, while you take it, and for 1 month after you stop taking it. You can either discuss effective birth control methods with your prescriber or go for a free visit to discuss birth control with another physician or family planning expert. Your prescriber can arrange this free visit, which will be paid for by the manufacturer.

You must use 2 separate forms of effective birth control because any method, including birth control pills and sterilization, can fail. There are only 2 reasons you would not need to use 2 separate methods of effective birth control:

1. You have had your womb removed by surgery (a hysterectomy).
2. You are absolutely certain you will not have genital-to-genital sexual contact with a male before, during, and for 1 month after Accutane treatment.

If you have sex at any time without using 2 forms of effective birth control, get pregnant, or miss your period, stop using Accutane and call your prescriber right away.

All patients should read the rest of this Medication Guide.

What are the signs of mental problems?

Tell your prescriber if, to the best of your knowledge, you or someone in your family has ever had any mental illness, including depression, suicidal behavior, or psychosis. Psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there. Also, tell your prescriber if you take medicines for any of these problems.

Stop using Accutane and tell your provider right away if you:

- Start to feel sad or have crying spells
- Lose interest in activities you once enjoyed
- Sleep too much or have trouble sleeping
- Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- Have a change in your appetite or body weight
- Have trouble concentrating
- Withdraw from your friends or family
- Feel like you have no energy
- Have feelings of worthlessness or inappropriate guilt
- Start having thoughts about hurting yourself or taking your own life (suicidal thoughts)

What is Accutane?

Accutane is used to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. These can be the size of pencil erasers or larger. If untreated, nodular acne can lead to permanent scars. However, because Accutane can have serious side effects, you should talk with your prescriber about all of the possible treatments for your acne, and whether Accutane's possible benefits outweigh its possible risks.

Who should not take Accutane?

- **Do not take Accutane if you are pregnant, plan to become pregnant, or become pregnant during Accutane treatment.** Accutane causes severe birth defects. All females should read the section "What are the important warnings for females taking Accutane?" for more information and warnings about Accutane and pregnancy.
- Do not take Accutane unless you completely understand its possible risks and are willing to follow all of the instructions in this Medication Guide.

Tell your prescriber if you or someone in your family has had any kind of mental problems, asthma, liver disease, diabetes, heart disease, osteoporosis (bone loss), weak bones, anorexia nervosa (an eating disorder where people eat too little), or any other important health problems. Tell your prescriber about any food or drug allergies you have had in the past. These problems do not necessarily mean you cannot take Accutane, but your prescriber needs this information to discuss if Accutane is right for you.

How should I take Accutane?

- You will get no more than a 30-day supply of Accutane at a time, to be sure you check in with your prescriber each month to discuss side effects.
- Your prescription should have a special yellow self-adhesive sticker attached to it. The sticker is YELLOW. If your prescription does not have this yellow self-adhesive sticker, call your prescriber. The pharmacy should not fill your prescription unless it has the yellow self-adhesive sticker.
- The amount of Accutane you take has been specially chosen for you and may change during treatment.
- You will take Accutane 2 times a day with a meal, unless your prescriber tells you otherwise. Swallow your Accutane capsules with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.
- If you miss a dose, just skip that dose. Do **not** take 2 doses the next time.
- You should return to your prescriber as directed to make sure you don't have signs of serious side effects. Because some of Accutane's serious side effects show up in blood tests, some of these visits may involve blood tests (monthly visits for female patients should always include a urine or serum pregnancy test).

What should I avoid while taking Accutane?

- **Do not get pregnant** while taking Accutane. See "What is the most important information I should know about Accutane?" and "What are the important warnings for females taking Accutane?"
- **Do not breast feed** while taking Accutane and for 1 month after stopping Accutane. We do not know if Accutane can pass through your milk and harm the baby.

- **Do not give blood** while you take Accutane and for 1 month after stopping Accutane. If someone who is pregnant gets your donated blood, her baby may be exposed to Accutane and may be born with birth defects.
- **Do not take vitamin A** supplements. Vitamin A in high doses has many of the same side effects as Accutane. Taking both together may increase your chance of getting side effects.
- **Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using Accutane and for at least 6 months after you stop.** Accutane can increase your chance of scarring from these procedures. Check with your prescriber for advice about when you can have cosmetic procedures.
- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. Accutane may make your skin more sensitive to light.
- **Do not use birth control pills that do not contain estrogen ("minipills").** They may not work while you take Accutane. Ask your prescriber or pharmacist if you are not sure what type you are using.
- **Talk with your doctor if you plan to take other drugs or herbal products**. This is especially important for patients using birth control pills and other hormonal types of birth control because the birth control may not work as effectively if you are taking certain drugs or herbal products. You should not take the herbal supplement St. John's Wort because this herbal supplement may make birth control pills not work as effectively.
- **Talk with your doctor if you are currently taking an oral or injected corticosteroid or anticonvulsant (seizure) medication prior to using Accutane.** These drugs may weaken your bones.
- **Do not share Accutane with other people.** It can cause birth defects and other serious health problems.
- **Do not take Accutane with antibiotics unless you talk to your prescriber.** For some antibiotics, you may have to stop taking Accutane until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain.

What are the possible side effects of Accutane?

Accutane has possible serious side effects

- **Accutane can cause birth defects, premature births, and death in babies** whose mothers took Accutane while they were pregnant. See "What is the most important information I should know about Accutane?" and "What are the important warnings for females taking Accutane?"
- **Serious mental health problems.** See "What is the most important information I should know about Accutane?"
- **Serious brain problems.** Accutane can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Accutane and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking Accutane have had seizures (convulsions) or stroke.
- **Abdomen (stomach area) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Accutane. Stop taking Accutane and call your prescriber if you get severe stomach, chest or bowel pain, trouble swallowing or painful swallowing, new or worsening heartburn, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine.

- **Bone and muscle problems.** Accutane may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your prescriber if you plan vigorous physical activity during treatment with Accutane. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are reports that some patients have had stunted growth after taking Accutane for acne as directed. There are also some reports of broken bones or reduced healing of broken bones after taking Accutane for acne as directed. No one knows if taking Accutane for acne will affect your bones. If you have a broken bone, tell your provider that you are taking Accutane. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens, stop taking Accutane and call your prescriber right away.
- **Hearing problems.** Some people taking Accutane have developed hearing problems. It is possible that hearing loss can be permanent. Stop using Accutane and call your prescriber if your hearing gets worse or if you have ringing in your ears.
- **Vision problems.** While taking Accutane you may develop a sudden inability to see in the dark, so driving at night can be dangerous. This condition usually clears up after you stop taking Accutane, but it may be permanent. Other serious eye effects can occur. Stop taking Accutane and call your prescriber right away if you have any problems with your vision or dryness of the eyes that is painful or constant.
- **Lipid (fats and cholesterol in blood) problems.** Many people taking Accutane develop high levels of cholesterol and other fats in their blood. This can be a serious problem. Return to your prescriber for blood tests to check your lipids and to get any needed treatment. These problems generally go away when Accutane treatment is finished.
- **Allergic reactions.** In some people, Accutane can cause serious allergic reactions. Stop taking Accutane and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Accutane may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

Serious permanent problems do not happen often. However, because the symptoms listed above may be signs of serious problems, if you get these symptoms, stop taking Accutane and call your prescriber. If not treated, they could lead to serious health problems. Even if these problems are treated, they may not clear up after you stop taking Accutane.

Accutane has less serious possible side effects

The common less serious side effects of Accutane are dry skin, chapped lips, dry eyes, and dry nose that may lead to nosebleeds. People who wear contact lenses may have trouble wearing them while taking Accutane and after therapy. Sometimes, people's acne may get worse for a while. They should continue taking Accutane unless told to stop by their prescriber.

These are not all of Accutane's possible side effects. Your prescriber or pharmacist can give you more detailed information that is written for health care professionals.

This Medication Guide is only a summary of some important information about Accutane. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any

concerns or questions about Accutane, ask your prescriber. Do not use Accutane for a condition for which it was not prescribed.

Active Ingredient: Isotretinoin.

Inactive Ingredients: 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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide Revised: June 2002

Pharmaceuticals

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-054

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Dermatologic and Dental Drug Products
HFD-540

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 18-662 SLR 054

Name of Drug: Accutane (isotretinoin) Capsules

Applicant: Hoffman-La Roche

Material Reviewed : SLR 054

Submission Dates: Feb. 20, 2004 **Receipt Dates: Feb. 24, 2004**

Background and Summary:

This submission contains amended final study reports containing *in vitro* and *in vivo* hormonal contraception interactions for 8 studies that were cross validated due to concerns about the analytical methods originally utilized. These studies were conducted to assess induction or inhibition potential of isotretinoin and its four major metabolites on hormonal contraceptives.

This submission also contains the 2 outstanding final study reports for the repeat norgestimate induction and inhibition studies which were repeated due to quality control measures which failed to meet the calibration curve acceptance.

[ ]

A comparison review of the Package Insert, Patient Information/Consent (for female patients concerning birth defects), Informed Consent/Patient Agreement (for all patients) and Medication Guide to the last approved labeling supplements S048 and S052 dated August 27, 2003 follows.

Review

A. PACKAGE INSERT:

1. Black Box CONTRAINDICATIONS AND WARNINGS:

No changes in this section with the exception of the proposed deletion of the statement "A drug interaction that decreased effectiveness of hormonal contraceptive has not been entirely ruled out for Accutane".

Clinical Pharmacology concludes to maintain the statement.

Division Director and Clinical Reviewer concur. However, the addition of " (see PRECAUTIONS: Drug Interactions)" will be added at the end of the statement.

2. DESCRIPTION: No changes
3. Clinical Pharmacology : No changes
Nodular Acne: No changes
4. Pharmacokinetics: No changes
5. Special Patient Populations: No Changes
6. Indications and Usage: No changes
7. Contraindications/Pregnancy/Allergic Reactions: No changes
8. WARNINGS: Psychiatric Disorders/Pseudotumor Cerebri/Pancreatitis/Lipids/Hearing Impairment/Hepatotoxicity/Inflammatory Bowel Disease/Skeletal/Vision Impairment: No Changes
9. PRECAUTIONS: General/Information for Patients and Prescribers: Hypersensitivity: No changes
10. PRECAUTIONS: Information for Patients and Prescribers: Drug Interactions: No changes except:
a. 3rd bullet Micro-dosed progesterone Preparations: Sponsor proposes deletion of statement "It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane"

Clinical Pharmacology review concludes to maintain the statement.

The Division Director and Clinical Reviewer concur.

b. Sponsor proposes addition of the following 2 bullets after 3rd bullet Micro-dosed progesterone Preparations:

- Norethindrone/ethinyl estradiol: In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving OrthoNovum [redacted] blets as an oral contraceptive agent, Accutane at the recommended dose of 1mg.kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol [redacted] and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Clinical Pharmacology concludes that this statement is acceptable and correct in the information provided.

The Division Director and Clinical Reviewer concur.

[redacted]

Clinical Pharmacology concludes that the proposed statement should be deleted. In vitro studies do not provide enough information. Conducting in vivo studies would be needed to provide more evidence based data.

The Division Director and Clinical Reviewer concur.

11. Laboratory Tests: No change
12. Pregnancy: Category X/Nursing Mothers: No change
13. Pediatric Use: No change
14. Geriatric Use: No Change
15. ADVERSE REACTIONS (all sections): No change
16 OVERDOSAGE: No change
17. DOSAGE AND ADMINISTRATION/ Boxed Information for Pharmacists: No change
18. HOW SUPPLIED/Storage: No change
19. REFERENCES: No change

B. Patient Information/Consent (for female patients concerning birth defects)

No changes in any section or numbered items.

C. Informed Consent/Patient Agreement (for all patients)

No changes in any section or numbered items.

D. Medication Guide: No changes in any section for text. However, the reference to OrthoNovum 7/7/7 in the PRECAUTIONS: Drug Interaction subsection, bullet #4 is recognized with the statement: OrthoNovum 7/7/7 is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.

This reference statement will be moved to the end of the package insert after References and is acceptable.

Conclusions

Proposed labeling changes submitted by sponsor and further Agency revisions as discussed above were communicated to the sponsor on August 23, 2004. The sponsor agreed to the labeling revisions as presented August 23, 2004.

Agreed to labeling is attached.

Recommendation:

Issue an Approval Letter for S 054.

Mary Jean Kozma-Fornaro
Chief, Project Management Staff

WITHHOLD 33 PAGE(S)

Draft labeling

B4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Jean Kozma Fornaro
8/24/04 01:09:30 PM
CSO