CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-503

Trade Name: Sotret

Generic Name: Isotretinoin Capsules, USP, 30mg

Sponsor: Ranbaxy Pharmaceuticals, Inc.

Approval Date: June 20, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 76-503

JUN 20 2003

Ranbaxy Pharmaceuticals, Inc.
Attention: Abha Pant
U.S. Agent for: Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 25, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sotret™ Capsules (Isotretinoin Capsules USP, 30mg).

Reference is also made to your amendments dated October 21, 2002; and February 12, February 24, May 8, and May 29, 2003. Reference is also made to the suitability petition submitted under Section 505(j)(2)(C) of the Act and approved on August 8, 2002, (02P-0161/CP1) permitting you to file this ANDA for a drug product that differs from the reference listed drug product (RLD). Specifically, you have requested approval for a strength of the reference drug product that differs from those approved by the agency for marketing by HLR Technology.

The listed drug (RLD) referenced in your application, Accutane® Capsules of HLR Technology (HLR), is subject to a period of exclusivity. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", HLR's three-year exclusivity with respect to labeling providing for the use of Accutane® Capsules in the pediatric patient population, (M-12), will expire on November 2, 2005. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of HLR's labeling which is the subject of pediatric exclusivity protection to be omitted from the labeling of products approved under Section 505(j). The BCPA also permits the incorporation of language in the labeling of products approved under Section 505(j) that informs health care practitioners that HLR's drug product has been approved for pediatric use. The agency has determined that the final printed labeling you have submitted is

in compliance with the BCPA with respect to pediatric use protected by exclusivity.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. Your Sotret™ Capsules, 30mg, can be expected to have the same therapeutic effect as that of an equivalent dose of the reference listed product upon which the agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert L. Lesko for 6/20/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

FINAL PRINTED LABELING

76-503

ISOTRETINOIN CAPSULES, USP
Rx only

CAUSES BIRTH DEFECTS

Bar Code

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS: Isotretinoin capsules must not be used by females who are pregnant. Although not every fetus exposed to isotretinoin capsules has resulted in a deformed child, there is an extremely high risk that a deformed infant can result if pregnancy occurs while taking isotretinoin capsules 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 isotretinoin capsules exposure, which fetus has been affected and which fetus has not been affected.

Major human fetal abnormalities related to isotretinoin capsules 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.

Isotretinoin capsules are contraindicated in females of childbearing potential unless the patient meets all of the following conditions:

- **Must NOT be pregnant or breast feeding.**
- **Must be capable of complying with the mandatory contraceptive measures required for isotretinoin capsules therapy and understand behaviors associated with an increased risk of pregnancy.**
- **Must be reliable in understanding and carrying out instructions.**

Isotretinoin capsules must be prescribed under the *Isotretinoin Medication Program Alerting Risks of Teratogenicity*™ (I.M.P.A.R.T.™).

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

1) Read the booklet entitled *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) *Guide to Best Practices*.

2) Sign and return the completed I.M.P.A.R.T. *Letter of Understanding* containing the following Prescriber Checklist:

- **I know the risk and severity of fetal injury/birth defects from isotretinoin capsules**
- **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 isotretinoin capsules therapy and for 1 month after stopping isotretinoin capsules. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with isotretinoin capsules 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 isotretinoin capsules treatment course, the I.M.P.A.R.T. procedures for isotretinoin capsules, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Isotretinoin Capsules Qualification Stickers**

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

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

After a single 80 mg oral dose of isotretinoin capsules 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 isotretinoin capsules 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:* Pediatric pharmacokinetic information related to the use of isotretinoin capsules after single and multiple doses is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

INDICATIONS AND USAGE: *Severe Recalcitrant Nodular Acne:* Isotretinoin capsules are 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, isotretinoin capsules should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, isotretinoin capsules are indicated only for those females who are not pregnant, because isotretinoin capsules 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 isotretinoin capsules. 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: Isotretinoin capsules are contraindicated in patients who are hypersensitive to this medication or to any of its components. Isotretinoin capsules 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:* Isotretinoin capsules may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Discontinuation of isotretinoin capsules 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 Isotretinoin Capsules).*

***Pseudotumor Cerebri:* Isotretinoin capsule 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 isotretinoin capsules 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.** Isotretinoin capsules should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Lipids: Elevations of serum triglycerides have been reported in patients treated with isotretinoin capsules. Marked elevations of serum triglycerides in excess of 800 mg/dL were reported in approximately 25% of patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules.[5]

Blood lipid determinations should be performed before isotretinoin capsules is given and then at intervals until the lipid response to isotretinoin capsules 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 isotretinoin capsules therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If isotretinoin capsules therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see

mIU/mL before receiving the initial isotretinoin capsules prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin capsules. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin capsules 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. The manufacturer will make available urine pregnancy test kits for female isotretinoin capsules patients for the initial, second and monthly testing during therapy.

- 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 isotretinoin capsules therapy, during isotretinoin capsules therapy, and for 1 month after discontinuing isotretinoin capsules 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 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 isotretinoin capsules. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports occurred while these patients were taking isotretinoin capsules. 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 Isotretinoin Capsules Survey and have been given the opportunity to enroll (see PRECAUTIONS).

The yellow self-adhesive Isotretinoin Capsules 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 Isotretinoin Capsules Qualification Stickers should also be used for male patients.

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

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

*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 isotretinoin capsules, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to Ranbaxy @ 1-866-431-8179 where a Ranbaxy Contraception Prevention Program Specialist will be available to discuss Ranbaxy pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

[illegible] should be prescribed only by prescribers who have demonstrated [illegible] recalcitrant nodular acne, are

The cardiovascular consequences of hypertriglyceridemia associated with isotretinoin capsules 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 isotretinoin capsules; 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules, the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease: Isotretinoin capsules have 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 isotretinoin capsules treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue isotretinoin capsules immediately (see ADVERSE REACTIONS: *Gastrointestinal*).

Skeletal: *Bone Mineral Density:* Effects of multiple courses of isotretinoin capsules on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (adjusted for body mass index).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin capsules population. While causality to isotretinoin capsules has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules. The effect of multiple courses of isotretinoin capsules on epiphyseal closure is unknown.

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

Corneal Opacities: Corneal opacities have occurred in patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules therapy [illegible] has persisted after therapy was discontinued. Because the onset in [illegible] problem and warned to be

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

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

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

***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 isotretinoin capsules, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to Ranbaxy @ 1-866-431-8179 where a Ranbaxy Contraception Prevention Program Specialist will be available to discuss Ranbaxy pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

Isotretinoin capsules 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 I.M.P.A.R.T. *Guide to Best Practices*, signed and returned the *completed* I.M.P.A.R.T. *Letter of Understanding*, and obtained yellow self-adhesive Isotretinoin Capsules Qualification Stickers. Isotretinoin capsules should not be prescribed or dispensed without a yellow self-adhesive Isotretinoin Capsules Qualification Sticker.

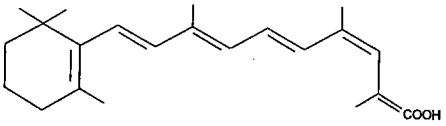
INFORMATION FOR PHARMACISTS:

ISOTRETINOIN CAPSULES MUST ONLY BE DISPENSED:

- **IN NO MORE THAN A 30-DAY SUPPLY**
- **ONLY ON PRESENTATION OF AN ISOTRETINOIN CAPSULES PRESCRIPTION WITH A YELLOW SELF- ADHESIVE ISOTRETINOIN CAPSULES QUALIFICATION STICKER**
- **WRITTEN WITHIN THE PREVIOUS 7 DAYS**
- **REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ISOTRETINOIN CAPSULES QUALIFICATION STICKER**
- **NO TELEPHONE OR COMPUTERIZED PRESCRIPTIONS ARE PERMITTED.**
- **AN ISOTRETINOIN CAPSULES MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME ISOTRETINOIN CAPSULES IS DISPENSED, AS REQUIRED BY LAW. THIS ISOTRETINOIN CAPSULES MEDICATION GUIDE IS AN IMPORTANT PART OF THE RISK MANAGEMENT PROGRAM FOR THE PATIENT.**

DESCRIPTION: Isotretinoin, a retinoid, is available as isotretinoin capsules in 30-mg soft gelatin capsules for oral administration. Each capsule contains butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil, hydrogenated vegetable oil, iron oxide black, soybean oil and white wax. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye system: 30 mg - FD&C Yellow No. 6, 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 isotretinoin capsules, 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 isotretinoin capsules 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 isotretinoin capsules 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, isotretinoin 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

Isotretinoin capsules 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.

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin capsules population. While causality to isotretinoin capsules has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules. The effect of multiple courses of isotretinoin capsules on epiphyseal closure is unknown.

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

Corneal Opacities: Corneal opacities have occurred in patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 Isotretinoin Capsules Pregnancy Prevention and Risk Management Programs consist of the *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) and the Isotretinoin Capsules Conception Prevention Program (CPP). I.M.P.A.R.T. should be followed for prescribing isotretinoin capsules with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) reading the booklet entitled *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) *Guide to Best Practices*, 2) signing and returning the completed I.M.P.A.R.T. *Letter of Understanding* containing the Prescriber Checklist, 3) a yellow self-adhesive Isotretinoin Capsules Qualification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Be Clever, Be Cautious, Be Certain,* should be used with each patient.

The following further describes each component:

1) The I.M.P.A.R.T. *Guide to Best Practices includes:* isotretinoin capsules 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 isotretinoin capsules prescription.

2) The I.M.P.A.R.T. *Letter of Understanding* attests that isotretinoin capsules prescribers understand that isotretinoin capsules is a teratogen, have read the I.M.P.A.R.T. *Guide to Best Practices*, understand their responsibilities in preventing exposure of pregnant females to isotretinoin capsules and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.

The Prescriber Checklist attests that isotretinoin capsules prescribers know the risk and severity of injury/birth defects from isotretinoin capsules; 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 isotretinoin capsules treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and use of qualified prescriptions with the yellow self-adhesive Isotretinoin Capsules Qualification Sticker.

3) The yellow self-adhesive Isotretinoin Capsules 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) Isotretinoin Capsules Contraception Prevention Program (CPP) is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The CPP includes information on the risks and benefits of isotretinoin capsules which is linked to the Isotretinoin Capsules Medication Guide dispensed by pharmacists with each prescription.

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

   The booklet for male patients, *Be Clever, Be Cautious, Be Certain Isotretinoin Risk Management Program for Men*, also includes information about male reproduction, a warning not to share isotretinoin capsules with others or to donate blood during isotretinoin capsules therapy and for 1 month following discontinuation of isotretinoin capsules.

   The booklet for female patients, *Be Clever, Be Cautious, Be Certain, Isotretinoin 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 Isotretinoin Capsules Survey; and a qualification checklist affirming the conditions under which female patients may receive isotretinoin capsules. 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 a video about the most common reasons for unplanned pregnancies.

General: Although an effect of isotretinoin capsules on bone loss is not established, physicians should use caution when prescribing isotretinoin capsules 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 isotretinoin capsules or following cessation of treatment with isotretinoin

After a single 80 mg oral dose of isotretinoin capsules 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 isotretinoin capsules 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:* Pediatric pharmacokinetic information related to the use of isotretinoin capsules after single and multiple doses is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

INDICATIONS AND USAGE: *Severe Recalcitrant Nodular Acne:* Isotretinoin capsules are 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, isotretinoin capsules should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, isotretinoin capsules are indicated only for those females who are not pregnant, because isotretinoin capsules 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 isotretinoin capsules. 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: Isotretinoin capsules are contraindicated in patients who are hypersensitive to this medication or to any of its components. Isotretinoin capsules 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:* Isotretinoin capsules may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Discontinuation of isotretinoin capsules 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 Isotretinoin Capsules).*

***Pseudotumor Cerebri:* Isotretinoin capsule 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 isotretinoin capsules 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.** Isotretinoin capsules should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Lipids: Elevations of serum triglycerides have been reported in patients treated with isotretinoin capsules. Marked elevations of serum triglycerides in excess of 800 mg/dL were reported in approximately 25% of patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules.[5]

Blood lipid determinations should be performed before isotretinoin capsules is given and then at intervals until the lipid response to isotretinoin capsules 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 isotretinoin capsules therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If isotretinoin capsules therapy is instituted, capsules while involved in these activities. While causality to isotretinoin capsules 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 isotretinoin capsules 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 Isotretinoin Capsules.* All patients should sign the Informed Consent/Patient Agreement.
- Females of childbearing potential should be instructed that they must not be pregnant when isotretinoin capsules therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting isotretinoin capsules, while taking isotretinoin capsules, and for 1 month after isotretinoin capsules has been stopped. They should also sign a consent form prior to beginning isotretinoin capsules therapy. They should be given an opportunity to enroll in the Isotretinoin Capsules Survey and to review the patient videotape provided by the manufacturer to the prescriber. It includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs. 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 isotretinoin capsules prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).
- Isotretinoin is found in the semen of male patients taking isotretinoin capsules, 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 isotretinoin capsules therapy is appropriate in this setting (see WARNINGS: *Psychiatric*).
- Patients should be informed that they must not share isotretinoin capsules 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 isotretinoin capsules.
- Patients should be reminded to take isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules, 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 isotretinoin capsules 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 isotretinoin capsules. Consideration should be given to discontinuation of isotretinoin capsules if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported. Isotretinoin capsules 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 isotretinoin capsules to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.

unknown. *Animal Studies:* In rats given 0.3 or 32 mg/kg/day of isotretinoin (1/6 to 5/6 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 isotretinoin capsules; 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules, the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease: Isotretinoin capsules have 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 isotretinoin capsules treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue isotretinoin capsules immediately (see ADVERSE REACTIONS: *Gastrointestinal*).

Skeletal: *Bone Mineral Density:* Effects of multiple courses of isotretinoin capsules on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (adjusted for body mass index).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin capsules population. While causality to isotretinoin capsules has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules. The effect of multiple courses of isotretinoin capsules on epiphyseal closure is unknown.

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

Corneal Opacities: Corneal opacities have occurred in patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 Isotretinoin Capsules Pregnancy Prevention and Risk Management Programs consist of the *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) and the Isotretinoin Capsules Conception Prevention Program (CPP). I.M.P.A.R.T. should be followed for prescribing isotretinoin capsules with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) reading the booklet entitled *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) *Guide to Best Practices,* 2) signing and returning the completed I.M.P.A.R.T. *Letter of Understanding* containing the Prescriber Checklist, 3) a yellow self-adhesive Isotretinoin Capsules Qualification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Be Clever, Be Cautious, Be Certain,* should be used with each patient.

The following further describes each component:

1) The I.M.P.A.R.T. *Guide to Best Practices includes:* isotretinoin capsules 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 isotretinoin capsules prescription.

2) The I.M.P.A.R.T. *Letter of Understanding* attests that isotretinoin capsules prescribers understand that isotretinoin capsules is a teratogen, have read the I.M.P.A.R.T. *Guide to Best Practices,* understand their responsibilities in preventing exposure of pregnant females to isotretinoin capsules and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.

The Prescriber Checklist attests that isotretinoin capsules prescribers know the risk and severity of injury/birth defects from isotretinoin capsules; 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 isotretinoin capsules treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and not contain an estrogen) may be an inadequate method of contraception during isotretinoin capsules 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with isotretinoin capsules. 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).

- *Phenytoin:* Isotretinoin capsules have 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 isotretinoin capsules. 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 isotretinoin capsules. 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. **Isotretinoin capsules use is associated with depression in some patients (see WARNINGS: *Psychiatric* 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 isotretinoin capsules prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin capsules (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 isotretinoin capsules 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 isotretinoin capsules is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin capsules 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 isotretinoin capsules has been established (see WARNINGS: *Hepatotoxicity*).
- *Glucose:* Some patients receiving isotretinoin capsules have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin capsules therapy, although no causal relationship has been established.
- *CPK:* Some patients undergoing vigorous physical activity while on isotretinoin capsules 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 capsules 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 capsules 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 capsules 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 capsules, 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 isotretinoin capsules 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 isotretinoin capsules.

Pediatric Use: The use of isotretinoin capsules in pediatric patients less than 12 years of age has not been studied. The use of isotretinoin capsules 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*).

Evidence supporting the use of isotretinoin capsules in this age group for severe recalcitrant nodular acne is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

In studies with isotretinoin capsules, 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

l a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course f isotretinoin capsules 4 months after the first course, two patients showed a decrease in mean mbar spine bone mineral density up to 3.25% (adjusted for body mass index).

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

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

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

ematurе Epiphyseal Closure: There are spontaneous reports of premature epiphyseal closure in acne tients receiving recommended doses of isotretinoin capsules. The effect of multiple courses of otretinoin capsules on epiphyseal closure is unknown.

sion Impairment: Visual problems should be carefully monitored. All isotretinoin capsules patients periencing visual difficulties should discontinue isotretinoin capsules treatment and have an ophthal- ological examination (see ADVERSE REACTIONS: *Special Senses*).

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

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

ECAUTIONS: The Isotretinoin Capsules Pregnancy Prevention and Risk Management Programs ısist of the *Isotretinoin Medication Program Alerting Risks of Teratogenicity* (I.M.P.A.R.T.) and the otretinoin Capsules Conception Prevention Program (CPP). I.M.P.A.R.T. should be followed for pre- ibing isotretinoin capsules with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) ıding the booklet entitled *Isotretinoin Medication Program Alerting Risks of Teratogenicity* M.P.A.R.T.) *Guide to Best Practices*, 2) signing and returning the completed I.M.P.A.R.T. *Letter of derstanding* containing the Prescriber Checklist, 3) a yellow self-adhesive Isotretinoin Capsules alification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Clever, Be Cautious, Be Certain,* should be used with each patient.

e following further describes each component:

The I.M.P.A.R.T. *Guide to Best Practices includes:* isotretinoin capsules 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 isotretinoin capsules prescription.

The I.M.P.A.R.T. *Letter of Understanding* attests that isotretinoin capsules prescribers understand that isotretinoin capsules is a teratogen, have read the I.M.P.A.R.T. *Guide to Best Practices,* under- stand their responsibilities in preventing exposure of pregnant females to isotretinoin capsules and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.

Prescriber Checklist attests that isotretinoin capsules prescribers know the risk and severity of ry/birth defects from isotretinoin capsules; know how to diagnose and treat the various presentations cne; know the risk factors for unplanned pregnancy and the effective measures for avoidance; will r the patient for, or provide, detailed pregnancy prevention counseling to help the patient have wledge and tools needed to fulfill their ultimate responsibility to avoid becoming pregnant; erstand and properly use throughout the isotretinoin capsules treatment course, the revised risk nagement procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and of qualified prescriptions with the yellow self-adhesive Isotretinoin Capsules Qualification Sticker.

The yellow self-adhesive Isotretinoin Capsules Qualification Sticker is used as documentation that he prescriber has qualified the female patient according to the qualification criteria (see boxed CON- TRAINDICATIONS AND WARNINGS).

sotretinoin Capsules Contraception Prevention Program (CPP) is a systematic approach to com- prehensive patient education about their responsibilities and includes education for contraception ompliance and reinforcement of educational messages. The CPP includes information on the risks nd benefits of isotretinoin capsules which is linked to the Isotretinoin Capsules Medication Guide lispensed by pharmacists with each prescription.

Male and female patients are provided with separate booklets. Each booklet contains information on sotretinoin capsules therapy, including precautions and warnings, an Informed Consent/Patient greement form, and a toll-free line which provides isotretinoin capsules information in English and panish.

he booklet for male patients, *Be Clever, Be Cautious, Be Certain Isotretinoin Risk Management Program for Men,* also includes information about male reproduction, a warning not to share sotretinoin capsules with others or to donate blood during isotretinoin capsules therapy and for 1 nonth following discontinuation of isotretinoin capsules.

he booklet for female patients, *Be Clever, Be Cautious, Be Certain, Isotretinoin Pregnancy Prevention and Risk Management Program for Women,* also includes a referral program that offers emales free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; second Patient Information/Consent form concerning birth defects, obtaining her consent to be eated within this agreement; an enrollment form for the Isotretinoin Capsules Survey; and a ualification checklist affirming the conditions under which female patients may receive isotretinoin apsules. In addition, there is information on the types of contraceptive methods, the selection and se of appropriate, effective contraception, and the rates of possible contraceptive failure; a toll-free ontraception counseling line; and a video about the most common reasons for unplanned regnancies.

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

nts may be at increased risk when participating in sports with repetitive impact where the risks of dylolisthesis with and without pars fractures and hip growth plate injuries in early and late scence are known. There are spontaneous reports of fractures and/or delayed healing in patients on treatment with isotretinoin capsules or following cessation of treatment with isotretinoin

- *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 isotretinoin capsules is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin capsules 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 isotretinoin capsules has been established (see WARNINGS: *Hepatotoxicity*).
- *Glucose:* Some patients receiving isotretinoin capsules have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin capsules therapy, although no causal relationship has been established.
- *CPK:* Some patients undergoing vigorous physical activity while on isotretinoin capsules 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 capsules 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 capsules 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 capsules 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 capsules, 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 isotretinoin capsules 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 isotretinoin capsules.

Pediatric Use: The use of isotretinoin capsules in pediatric patients less than 12 years of age has not been studied. The use of isotretinoin capsules 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*).

Evidence supporting the use of isotretinoin capsules in this age group for severe recalcitrant nodular acne is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

In studies with isotretinoin capsules, 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 isotretinoin capsules 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%).

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 isotretinoin capsules, and the postmarketing experience. The relationship of some of these events to isotretinoin capsules therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving isotretinoin capsules 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.

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

The recommended dosage range for isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules, even in low doses, has not been studied, and is not recommended. It is important that isotretinoin capsules be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of isotretinoin capsules 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. Isotretinoin Capsules 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: Isotretinoin capsules must only be dispensed in no more than a 30-day supply and only on presentation of an isotretinoin capsules prescription with a yellow

15. I understand that the yellow self-adhesive Isotretinoin Capsules Qualification Sticker on my prescription for isotretinoin capsules means that I am qualified to receive a isotretinoin capsules prescription, because I:

- have had 2 negative urine or serum pregnancy tests before receiving the initial isotretinoin capsules 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 isotretinoin capsules 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 Isotretinoin Capsules Survey and given the opportunity to enroll.

Initial:_____

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

Initial:_____

I now authorize my prescriber _____ to begin my treatment with isotretinoin capsules.

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 treatment described above and the risk to females of childbearing potential. I have asked the patient if she has any questions regarding her treatment with isotretinoin capsules 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 isotretinoin capsules if there is anything that you do not understand about all the information you have received about using isotretinoin capsules.

1. I, _____
(Patient's Name)
understand that isotretinoin capsules 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 isotretinoin capsules. 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 isotretinoin capsules or soon after stopping isotretinoin capsules, 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 isotretinoin capsules have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people have 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 isotretinoin capsules becoming aggressive or violent. No one knows if isotretinoin capsules caused these behaviors or if they would have happened even if the person did not take isotretinoin capsules. Some people have had other signs of depression while taking isotretinoin capsules (see #7 below).**

   Initials: _____

5. **Before I start taking isotretinoin capsules, 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 isotretinoin capsules, 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 isotretinoin capsules, I agree to stop using isotretinoin capsules and tell my prescriber right away if any of the following happens. 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)

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 isotretinoin capsules, even in low doses, has not been studied, and is not recommended. It is important that isotretinoin capsules be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of isotretinoin capsules 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. Isotretinoin Capsules Dosing by Body Weight (Based on Administration With Food)

Body Weight		Total mg/day		
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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: Isotretinoin capsules must only be dispensed in no more than a 30-day supply and only on presentation of an isotretinoin capsules prescription with a yellow self-adhesive Isotretinoin Capsules Qualification Sticker written within the previous 7 days. **REFILLS REQUIRE A NEW WRITTEN PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ISOTRETINOIN CAPSULES QUALIFICATION STICKER WITHIN THE PREVIOUS 7 DAYS.** No telephone or computerized prescriptions are permitted.

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

HOW SUPPLIED: Soft gelatin capsules, 30 mg (golden yellow), imprinted "RR". Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 63304-447-77).

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

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6. Ellis CN, Madison KC, Pennes DR, Martel W, Voorhees JJ. Isotretinoin therapy is associated with early skeletal radiographic changes. *J Am Acad Dermatol* 10:1024-1029, 1984.
7. Dicken CH, Connolly SM. Eruptive xanthomas associated with isotretinoin (13-*cis*-retinoic acid). *Arch Dermatol* 116:951-952, 1980.
8. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol* 10:490-496, 1984.

PATIENT INFORMATION/CONSENT

(for female patients concerning birth defects):

To be completed by patient, her parent or guardian* 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. **Do not sign this consent and do not take isotretinoin capsules if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and understand 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 isotretinoin capsules in any amount even for short periods of time. This is why I must not be pregnant while taking isotretinoin capsules.

   Initial:_____

2. I understand that I must not take isotretinoin capsules 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 isotretinoin capsules.

   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 injectable/implantable/insertable hormonal birth control products are among the most effective forms of birth control. However, any single 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 injections.

   Initial:_____

6. I will talk with my prescriber about any drugs or herbal products I plan to take during my isotretinoin capsules 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, injectable/implantable/insertable hormonal birth control products, and an IUD (intrauterine device).

   Barrier: Diaphragm, latex condoms, and cervical caps. Each must be used with a spermicide

aggressive or violent. No one knows if isotretinoin capsules caused these behaviors or if they would have happened even if the person did not take isotretinoin capsules. Some people have had other signs of depression while taking isotretinoin capsules (see #7 below).

Initials: _____

5. **Before I start taking isotretinoin capsules, 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 isotretinoin capsules, 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 isotretinoin capsules, I agree to stop using isotretinoin capsules and tell my prescriber right away if any of the following happens. 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 isotretinoin capsules into get a new prescription for isotretinoin capsules, to check my progress, and to check for signs of side effects.**

   Initials: _____

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

   Initials: _____

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

    Initials: _____

11. **I have read the *Patient Product Information, Important Information Concerning Your Treatment with Isotretinoin Capsules,* and other materials my prescriber gave me containing important safety information about isotretinoin capsules. I understand all the information I received.**

    Initials: _____

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

    Initials:_____

I now authorize my prescriber _____to begin my treatment with isotretinoin capsules.

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 isotretinoin capsules treatment, including its benefits and risks
- given the patient the appropriate educational materials, *Be Clever, Be Cautious, Be Certain,* for isotretinoin capsules and asked the patient if he/she has any questions regarding his/her treatment with isotretinoin capsules
- answered those questions to the best of my ability
- placed the yellow self-adhesive Isotretinoin Capsules Qualification Sticker on the prescription.

Prescriber Signature: _____ Date: _____

MEDICATION GUIDE:

Read this Medication Guide every time you get a prescription or a refill for isotretinoin capsules. 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 isotretinoin capsules?

Isotretinoin capsules is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics. However, isotretinoin capsules can cause serious side effects. Before starting isotretinoin capsules, discuss with your prescriber how bad your acne is, the possible benefits of isotretinoin capsules, and its possible side effects, to decide if isotretinoin capsules are 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 isotretinoin capsules.

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

1. **Birth defects. Isotretinoin capsules 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 isotretinoin capsules if you are pregnant or plan to become preg-

cation. *J Am Acad Dermatol* 24:495-500, 1991.

3. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-*cis*-retinoic acid: evaluation of sebum production and the clinical response in a multipledose trial. *J Am Acad Dermatol* 3:602-611, 1980.

4. Jones H, Blanc D, Cunliffe WJ. 13-*cis*-retinoic acid and acne. *Lancet* 2:1048-1049, 1980.

5. Katz RA, Jorgensen H, Nigra TP. Elevation of serum triglyceride levels from oral isotretinoin in disorders of keratinization. *Arch Dermatol* 116:1369-1372, 1980.

6. Ellis CN, Madison KC, Pennes DR, Martel W, Voorhees JJ. Isotretinoin therapy is associated with early skeletal radiographic changes. *J Am Acad Dermatol* 10:1024-1029, 1984.

7. Dicken CH, Connolly SM. Eruptive xanthomas associated with isotretinoin (13-*cis*-retinoic acid). *Arch Dermatol* 116:951-952, 1980.

8. Strauss JS, Rapini RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol* 10:490-496, 1984.

PATIENT INFORMATION/CONSENT

(for female patients concerning birth defects):

To be completed by patient, her parent or guardian* 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. **Do not sign this consent and do not take Isotretinoin capsules if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and understand 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 isotretinoin capsules in any amount even for short periods of time. This is why I must not be pregnant while taking isotretinoin capsules.

   Initial:_____

2. I understand that I must not take Isotretinoin capsules 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 isotretinoin capsules.

   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 injectable/implantable/insertable hormonal birth control products are among the most effective forms of birth control. However, any single 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 injections.

   Initial:_____

6. I will talk with my prescriber about any drugs or herbal products I plan to take during my isotretinoin capsules 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, 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 and pregnancy testing from a doctor or other family planning expert. My isotretinoin capsules prescriber can give me an Isotretinoin Capsules 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 isotretinoin capsules.

   Initial:_____

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

    Initial:_____

11. I understand that I should not start taking isotretinoin capsules 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 Isotretinoin Capsules.* My prescriber gave me and asked me to watch the video 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 isotretinoin capsules 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 Isotretinoin Capsules Survey and explained to me how important it is to take part in the Isotretinoin Capsules Survey.

    Initial:_____

9

Initials: _____

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

    Initials: _____

11. **I have read the *Patient Product Information, Important Information Concerning Your Treatment with Isotretinoin Capsules,* and other materials my prescriber gave me containing important safety information about isotretinoin capsules. I understand all the information I received.**

    Initials: _____

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

    Initials:_____

I now authorize my prescriber _____to begin my treatment with isotretinoin capsules.

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 isotretinoin capsules treatment, including its benefits and risks
- given the patient the appropriate educational materials, *Be Clever, Be Cautious, Be Certain,* for isotretinoin capsules and asked the patient if he/she has any questions regarding his/her treatment with isotretinoin capsules
- answered those questions to the best of my ability
- placed the yellow self-adhesive Isotretinoin Capsules Qualification Sticker on the prescription.

Prescriber Signature: _____ Date: _____

MEDICATION GUIDE:

Read this Medication Guide every time you get a prescription or a refill for isotretinoin capsules. 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 Isotretinoin capsules?

Isotretinoin capsules is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics. However, isotretinoin capsules can cause serious side effects. Before starting isotretinoin capsules, discuss with your prescriber how bad your acne is, the possible benefits of isotretinoin capsules, and its possible side effects, to decide if isotretinoin capsules are 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 isotretinoin capsules.

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

1. **Birth defects. Isotretinoin capsules 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 isotretinoin capsules if you are pregnant or plan to become pregnant while you are taking isotretinoin capsules. Do not get pregnant for 1 month after you stop taking isotretinoin capsules. Also, if you get pregnant while taking isotretinoin capsules, 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 Isotretinoin capsules?"

2. **Mental problems and suicide.** Some patients, while taking isotretinoin capsules or soon after stopping isotretinoin capsules, 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 isotretinoin capsules 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 isotretinoin capsules becoming aggressive or violent. No one knows if isotretinoin capsules caused these behaviors or if they would have happened even if the person did not take isotretinoin capsules.

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

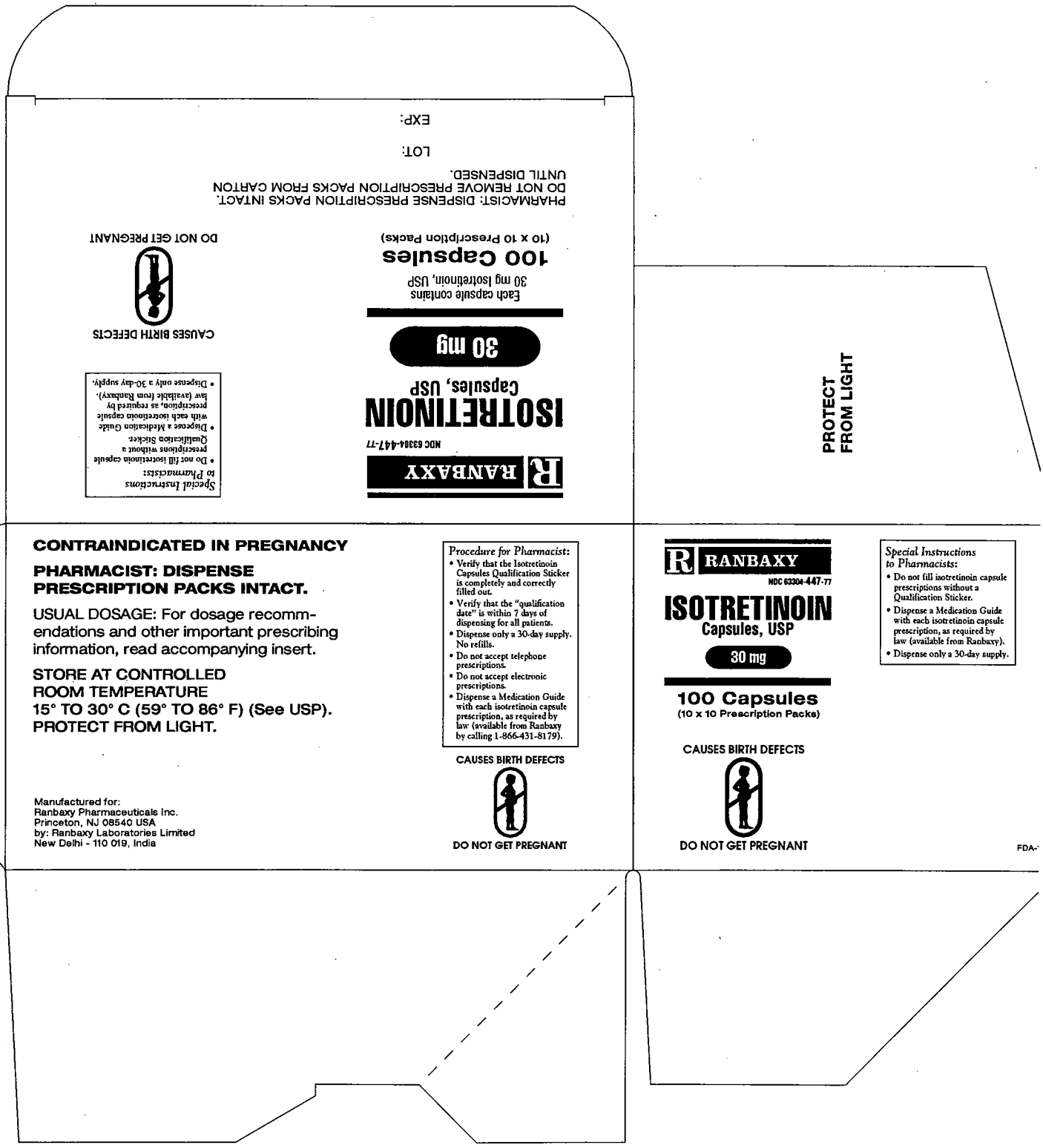
   For other possible serious side effects of isotretinoin capsules, see "What are the possible side effects of isotretinoin capsules?" in this Medication Guide.

What are the important warnings for females taking Isotretinoin capsules?

You must not become pregnant while taking isotretinoin capsules, or for 1 month after you stop taking isotretinoin capsules. Isotretinoin capsules can cause severe birth defects in babies of women who take it while they are pregnant, even if they take isotretinoin capsules 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 isotretinoin capsules. Taking isotretinoin capsules also increases the chance of miscarriage and premature births.

Female patients will not get their first prescription for isotretinoin capsules unless there is proof they have had 2 negative pregnancy tests. The first test must be done when your prescriber decides to prescribe isotretinoin capsules. The second pregnancy test must be done during the first 5 days of the menstrual period right before starting isotretinoin capsules 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 isotretinoin capsules unless there is proof that they have had a negative pregnancy test.

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



EXP:

LOT:

PHARMACIST: DISPENSE PRESCRIPTION PACKS INTACT.
DO NOT REMOVE PRESCRIPTION PACKS FROM CARTON
UNTIL DISPENSED.

(10 x 10 Prescription Packs)

100 Capsules

Each capsule contains
30 mg Isotretinoin, USP

30 mg

ISOTRETINOIN
Capsules, USP

NDC 63304-447-77

RANBAXY

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

Special Instructions to Pharmacists:
- Do not fill isotretinoin capsule prescriptions without a Qualification Sticker.
- Dispense a Medication Guide with each isotretinoin capsule prescription, as required by law (available from Ranbaxy).
- Dispense only a 30-day supply.

PROTECT FROM LIGHT

CONTRAINDICATED IN PREGNANCY

PHARMACIST: DISPENSE PRESCRIPTION PACKS INTACT.

USUAL DOSAGE: For dosage recommendations and other important prescribing information, read accompanying insert.

STORE AT CONTROLLED ROOM TEMPERATURE
15° TO 30° C (59° TO 86° F) (See USP).
PROTECT FROM LIGHT.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

Procedure for Pharmacist:
- Verify that the Isotretinoin Capsules Qualification Sticker is completely and correctly filled out.
- Verify that the "qualification date" is within 7 days of dispensing for all patients.
- Dispense only a 30-day supply. No refills.
- Do not accept telephone prescriptions.
- Do not accept electronic prescriptions.
- Dispense a Medication Guide with each isotretinoin capsule prescription, as required by law (available from Ranbaxy by calling 1-866-431-8179).

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

RANBAXY
NDC 63304-447-77

ISOTRETINOIN
Capsules, USP

30 mg

100 Capsules
(10 x 10 Prescription Packs)

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

FDA-

NDC 63304-447-11
ISOTRETINOIN
Capsule, USP
30 mg
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

NDC 63304-447-11
ISOTRETINOIN
Capsule, USP
30 mg
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

NDC 63304-447-11
ISOTRETINOIN
Capsule, USP
30 mg
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

NDC 63304-447-11
ISOTRETINOIN
Capsule, USP
30 mg
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

00000000

NDC 63304-447-11
ISOTRETINOIN
Capsule, USP
30 mg
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India

LOT:

EXP.:

0377

SEAL TAB
to be placed
here

PATIENT:
READ INFORMATION CAREFULLY

PHARMACISTS:
DISPENSE INTACT
PLACE PRESCRIPTION LABEL HERE

10 Capsules
Prescription Pack

Rx only

Each capsule contains 30 mg Isotretinoin, USP

30 mg

ISOTRETINOIN
Capsules, USP

RANBAXY

NDC 63304-447-11

00000000

30 mg

ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your prescriber.

This package provides **reminders** of important safety facts about isotretinoin capsules, but it does **not** contain all the information that you need to know. It is important for you to know how to take isotretinoin capsules correctly and what side effects to watch for.

Read all the information you get about isotretinoin capsules from your prescriber and pharmacist, including the **Medication Guide** provided with this package.

The prescription you got at your prescriber's office should have had a special yellow self-adhesive sticker on it. The sticker is YELLOW. If your prescriptions for isotretinoin capsules do not have this yellow self-adhesive sticker, call your prescriber. The pharmacy should not fill prescriptions for isotretinoin capsules unless they have the yellow self-adhesive sticker.

You should read, understand and sign an **Informed Consent/Patient Agreement** before you take isotretinoin capsules. Contact your prescriber if you have not signed this form (male patients must sign one form and female patients must sign two forms).

Never share isotretinoin capsules because it can cause serious side effects including severe birth defects.

Special Warning for Female Patients

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

Isotretinoin capsules cause birth defects. Do NOT take isotretinoin capsules if you are pregnant.
It is very important for you to read and understand the information about preventing pregnancy on the back of this package, in the Medication Guide, and in the materials given to you by your prescriber. If you do not have the Medication Guide, and a video and the *Be Clever, Be Cautious, Be Certain* booklet about pregnancy prevention, don't start taking isotretinoin capsules. Call your prescriber.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do **not** take isotretinoin capsules until your questions have been answered by your prescriber.

Important Information for All Patients

Before you start taking isotretinoin capsules, tell your prescriber if you:
- Are currently taking an oral or injected corticosteroid or an anticonvulsant (seizure) medication.
- Take part in sports where you are more likely to break a bone.
- Have anorexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.

Mental problems and suicide
Some patients have become depressed or developed other serious mental problems while they were taking isotretinoin capsules or shortly after stopping isotretinoin capsules. Some patients taking isotretinoin capsules have had thoughts of ending their own lives (suicidal thoughts).

FEMALE PATIENTS: DO NOT GET PREGNANT 30 mg

Isotretinoin Capsules Cause Serious Birth Defects

Highlights of Warning to Female Patients.

(It is **important** to watch the video and read all information in the ***Be Clever, Be Cautious, Be Certain*** booklet given to you by your prescriber).

- ▲ You MUST NOT take **isotretinoin** capsules if you are pregnant because any amount can cause severe birth **defects, even for short periods during pregnancy.**
- ▲ You MUST NOT become pregnant while taking isotretinoin capsules, or for 1 month after you stop taking isotretinoin capsules.
- ▲ You will not get your first prescription for isotretinoin capsules until there is proof you have had 2 negative pregnancy tests as instructed by your prescriber (a negative test means that it does not show pregnancy).
- ▲ You cannot get monthly refills for isotretinoin capsules unless there is proof that you have had a negative pregnancy test every month during isotretinoin capsules treatment.
- ▲ Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of contraception must be used at the same time for at least 1 month before beginning therapy, during therapy, and for 1 month after isotretinoin capsules therapy has stopped.
- ▲ Stop taking isotretinoin capsules right away and call your prescriber immediately if you have sex without birth control, miss your period or become pregnant while you are taking isotretinoin capsules. If you get pregnant in the month after you have stopped isotretinoin capsules treatment, call your prescriber immediately.

or if they would have happened even if the person did not take isotretinoin capsules.

Stop taking isotretinoin capsules and call your prescriber right away if you:

- Start to feel sad or have crying spells.
- Lose interest in activities you have 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).

Tell your prescriber if you or someone in your family has ever had a mental illness or if you take any medicines for a mental illness (for example, depression).

Other serious side effects to watch for

Stop taking isotretinoin capsules and call your prescriber if you develop any of the problems on this list or any other unusual or severe problems. If not treated, they could lead to serious health problems. Serious permanent problems do not happen often.

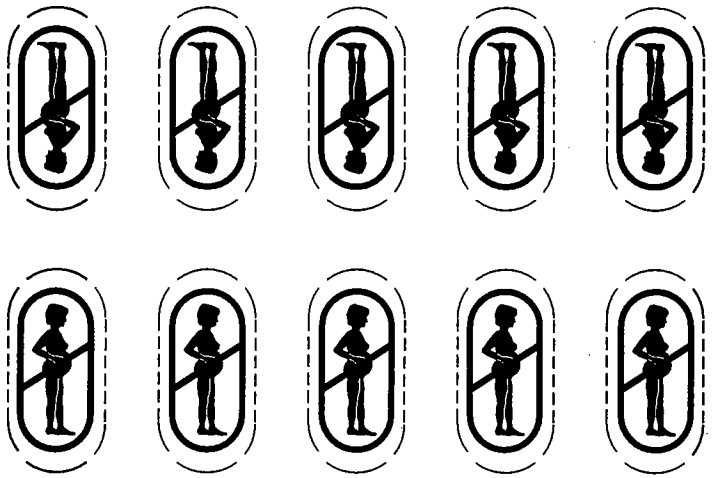
- Headaches, nausea, vomiting, blurred vision (increased brain pressure).
- Severe stomach pain, diarrhea, rectal bleeding, or trouble swallowing.
- Yellowing of your skin or eyes and/or dark urine.
- Changes in hearing.
- Allergic reactions (if you know you are sensitive to "parabens", tell your prescriber because it is a preservative in the gelatin capsule of isotretinoin capsules).
- Bone or muscle pain.
- Vision changes, including trouble seeing at night (this can start suddenly, so be very careful when driving or operating any vehicle at night).
- Persistent fever, chills, or sore throat.

Other important information is found in the Medication Guide and in the booklet from your prescriber:

- Common side effects that are not serious but that you should tell your prescriber about.
- How to take isotretinoin capsules.
- Things to avoid during isotretinoin capsules treatment.
- Ways to get more information if you need it.

YOU MUST NOT TAKE ISOTRETINOIN CAPSULES IF YOU ARE PREGNANT OR MAY BECOME PREGNANT DURING TREATMENT.

2. Grasp the paper-foil TAB - pull and carefully tear the board along perforation to free each capsule. See figure A on reverse side.



3. Keep package intact so that it will continue to provide the important information you should know as you take isotretinoin capsules.

LOT: EXP:

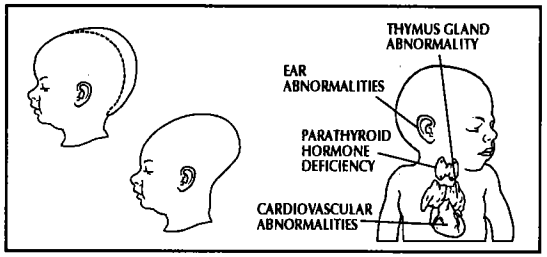
area

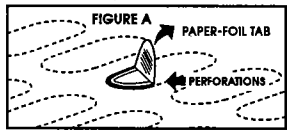
FEMALE PATIENTS: DO NOT GET PREGNANT

30 mg

Very severe birth defects have occurred with isotretinoin capsules use including:

- ▲ **Severe Internal Defects:** defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- ▲ **Severe External Defects:** defects that you can see—such as low-set, deformed or absent ears, wide set eyes, depressed bridge of nose, enlarged head and small chin.

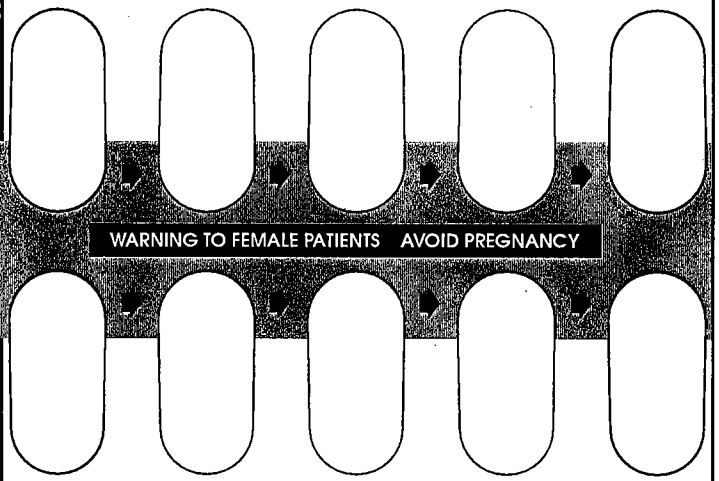




STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30° C (59° TO 86° F) (See USP). PROTECT FROM LIGHT.

WARNING TO FEMALE PATIENTS ISOTRETINOIN CAPSULES CAUSE SEVERE BIRTH DEFECTS.

PUSH THROUGH HERE



PUSH THROUGH HERE

1. DIRECTIONS FOR REMOVING EACH CAPSULE: Push through at arrow. Fold back and crease to form a PULL TAB on reverse side. Proceed to Step 2 on reverse side.

YOU MUST NOT TAKE ISOTRETINOIN CAPSULES IF YOU ARE PREGNANT OR MAY BECOME PREGNANT DURING TREATMENT.

This panel will be printed on the *inside* of the top opening flap of each unit dose box.

Procedure for Pharmacist:

- Verify that the Isotretinoin Capsules Qualification Sticker is completely and correctly filled out.
- Verify that the "qualification date" is within 7 days of dispensing for all patients.
- Dispense only a 30-day supply. No refills.
- Do not accept telephone prescriptions.
- Do not accept electronic prescriptions.
- Dispense a Medication Guide with each isotretinoin capsule prescription, as required by law (available from Ranbaxy by calling 1-866-431-8179).

0383

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

CSO LABELING REVIEW(S)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-503

Date of Submission: September 25, 2002
February 12, 2003
May 8, 2003
May 29, 2003

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Isotretinoin Capsules USP, 30 mg

Proprietary Name: Sotret™ Capsules

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 final printed Labels and Labeling? Yes

1. UNIT DOSE BLISTER CARD (1 X 10) –*Satisfactory in FPL as of the February 12, 2003* (Vol 2.2, 2.3,2.4; pg. 158)

2. CARTON - 100s (10 x 10) – *Satisfactory in FPL as of the February 12, 2003 submission* (Vol. 2.2,2.3,2.4; pg.159)

3. INSERT –*Satisfactory in FPL as of the February 12, 2003 submission* (Revised Feb. 2003,Vol. 2.2,2.3,2.4; pg.161)

4. ISOTRETINOIN MEDICATION PROGRAM ALERTING THE RISKS OF TERATOGENICITY IMPART™ Guide to Best Practices - *Satisfactory in FPL as of the February 12, 2003 submission (Vol 2.2,2.3,2.4; pg.163)*

5. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN
SOTRET PROGRAM TO PREVENT PREGNANCY AND RISK MANAGEMENT PROGRAM FOR WOMEN - *Satisfactory in FPL as of the February 12, 2003 submission (Vol 2.2,2.3, 2.4; pg. 164)*

6. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN SOTRET™ (isotretinoin) RISK MANAGEMENT FOR MEN – *Satisfactory in FPL as of the February 12, 2003 submission. (Vol. 2.2,2.3,2.4; pg.165)*

7. RECOGNIZING PSYCHIATRIC DISORDERS IN ADOLESCENTS AND YOUNG ADULTS: A Guide For Prescribers Of Sotret (Isotretinoin) - *Satisfactory in FPL as of the February 12, 2003 submission. (Vol. 2.2,2.3,2.4; pg. 166)*

8. SOTRET QUALIFICATION STICKER – *Satisfactory in FPL as of the February 12, 2003 submission. (Vol. 2.2,2.3,2.4; pg. 174)*

9. PRESCRIBING PROCEDURES FOR SOTRET™ (ISOTRETINOIN) - *Satisfactory in FPL as of the February 12, 2003 submission. (Vol. 2.2,2.3,2.4; pg. 167)*

10. DISPENSING PROCEDURES FOR SOTRET™ (ISOTRETINOIN) CAPSULES - Satisfactory in FPL as of the February 12, 2003 submission. *(Vol. 2.2,2.3,2.4; pg. 171)*

11. MEDICATION GUIDE - *Satisfactory in FPL as of the February 12, 2003 submission. (Vol. 2.2,2.3,2.4; pg. 162)*

12. LETTER OF UNDERSTANDING TO PRESCRIBERS –*Satisfactory in FPL as of the May 8, 2003 submission* (Vol 3.1, Attachment 1)

13. ISOTRETINOIN SURVEY FORM - *Satisfactory in FPL as of the May 8, 2003 submission.*(Vol 3.1, Attachment 3)

14. ISOTRETINOIN SURVEY FORM (For Females Only) - *Satisfactory in FPL as of the May 8, 2003 submission.*(Vol 3.1, Attachment 2)

15. INFORMED CONSENT/PATIENT AGREEMENT (All Patients) - *Satisfactory in FPL as of the May 8, 2003 submission* (Vol 3.1, Attachment 5)

16. INFORMED CONSENT/PATIENT AGREEMENT (for female patients) - *Satisfactory in FPL as of the May 8, 2003 submission* (Vol 3.1, Attachment 4)

17. QUALIFICATION CHECKLIST- *Satisfactory in FPL as of the May 8, 2003 submission* (Vol 3.1, Attachment 6)

18. ISOTRETINOIN PRESCRIPTION COMPLIANCE SURVEY – Satisfactory as of January 8, 2003 for Ranbaxy's 10 mg, 20 mg and 40 mg under ANDA 76-041

19. DISPENSING GUIDE - *Satisfactory in FPL as of the February 19, 2003 (Vol. 2.2,2.3,2.4; pg. 175)*

20. VIDEO SCRIPT -*Acceptable as of the May 8, 2003 submission. (Vol 3.1, Attachment 7)*

Revisions needed post-approval:

1. GENERAL - Revise storage temperature to Store at 20-25 ° C (68 - 77 ° F)
   [see USP Controlled Room Temperature]
   Ranbaxy has provided a commitment to revise their storage temperature at time of next printing.

2. INSERT
   ADVERSE REACTIONS-Musculoskeletal, add a line space above subsection.

3. ISOTRETINOIN MEDICATION PROGRAM ALERTING THE RISKS OF TERATOGENICITY IMPART™ Guide to Best Practices- CONTRAINDICATIONS AND WARNINGS, Information for Patients, last sentence- "A Sotret" instead of ~~_____~~

BASIS OF APPROVAL:

Patent Data – NDA 18-662

No	Expiration	Use Code	Use	File
		There are no unexpired patents pending		

Exclusivity Data - NDA 18-662

Code/sup	Expiration	Use Code	Description	Labeling Impact
M-12	May 2, 2005		Waxman-Hatch exclusivity	Used pediatric labeling disclaimer statement in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections
PED	Nov 2, 2005			" "

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Accutane Capsules
NDA Number: 18-662/S-051
NDA Drug Name: Isotretinoin Capsules
NDA Firm: Hoffman-La Roche Inc.
Date of Approval of NDA Insert and supplement #-51:June 20, 2002
Has this been verified by the MIS system for the NDA? Yes No
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Blister Labels: Side-by-side comparison
Basis of Approval for the Unit Dose Carton Labeling: Side-by-side comparison

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?	X		
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The USP recommends that this product be stored in tight containers protected from light. Do the proposed blisters and carton labeling satisfy this recommendation?
   The answer to your question is "yes".
   USP <671> water permeation rate: pass the test.
   Liang-Lii Huang, Ph.D.
   Review chemist

2. Because this drug product is packaged in what would be considered unit-of-use packaging, the blisters should be child-resistant. Is the packaging child-resistant?
   The answer to your question #2 is "yes".
   Unit dose container with Child resistant blister lidding.
   Liang-Lii Huang, Ph.D.
   Review chemist

FOR THE RECORD:

1. Labeling review based on the approved labeling for the RLD, (Accutane (NDA 18-662/S-051) – Hoffman La Roche Inc.; approved in draft June 20, 2002). The review of the Psychiatric brochure is based on the labeling approved in S-046 February 15, 2002. The information on which the Waxman-Hatch exclusivity is based is contained in S-043 approved May 2, 2002.

2. The Division of Medication Errors and Technical Support has no objections to the use of the proprietary name Sotret for the 10 mg, 20 mg and 40 mg. (ANDA 76-041).

3. Packaging

   The RLD packages its product in Unit dose wallets of 10 packaged in cartons of 100.

   The applicant proposes to market its product in unit dose blisters of clear film of ' ——— with paper foil, laminate backing. (Vol. A.1.14; Section XIII; p.4210) Because this product is packaged as unit-of -use packaging, meaning it can dispensed directly to the patient unaltered, and it is not one of the exceptions listed in the Poison Prevention Packaging Act of 1970 regulations, it must be in child resistant packaging.
   The firm has ensured that the unit dose packaging is child resistant.
   The chemist, Huang, Liang-Li has confirmed that it is child resistant packaging.

4. Labeling

   The firm has differentiated its product strengths by using different color contrast on their carton labeling. (ANDA 76-041, 10 mg, 20 mg, and 40 mg)
   Because this is a teratogenic drug product, special differentiation to avoid pregnancy is found throughout the labeling.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).
   The 30 mg capsules are golden yellow, imprinted "RR".

6. Manufacturer

Ranbaxy Laboratories Limited
India

7. Inactive Ingredients

There does not appear to be a discrepancy in inactives between the labeling and the C&C Statements. (Vol. A. 1.14; Section VII; p.3936)
The amount of elemental iron contained in the color additive (black iron oxide) does not exceed ——
(Vol B 2.1 p. 004)

8. USP Issues

USP – Preserve in tight containers, protected from light.
RLD – Store at controlled room temperature, 59 - 86°F (15 - 30°C). Protect from light.
ANDA – Store at controlled room temperature, 59 - 86°F (15 - 30°C). See USP. Protect from light.
The firm has been asked to change storage temperature to Store at 20-25 ° C (68 - 77 ° F) [see USP Controlled Room Temperature] post approval].

9. Bioequivalence issues –Satisfactory 1/29/03

10. Patent/Exclusivity Issues

Patent Data – NDA 18-662

No	Expiration	Use Code	Use	File
		There are no unexpired patents pending		

Exclusivity Data - NDA 18-662

Code/sup	Expiration	Use Code	Description	Labeling Impact
M-12	May 2, 2005		Waxman-Hatch exclusivity	Used pediatric labeling disclaimer statement in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections
PED	Nov 2, 2005			" "

The changes in labeling resulting from this exclusivity are as follows:

i. CLINICAL PHARMACOLOGY (Special Patient Populations) - Revise the subsection to read,

Pediatric pharmacokinetic information related to the use of isotretinoin after single and multiple doses is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

ii. PRECAUTIONS (Pediatric Use) - Revise this subsection to read:

The use of isotretinoin in pediatric patients less than 12 years of age has not been studied. The use of isotretinoin 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*).

Evidence supporting the use of isotretinoin in this age group for severe recalcitrant nodular acne is approved for Hoffman La-Roche's isotretinoin capsules. However, due to Hoffman La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

In studies with isotretinoin, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased...

Date of Review:	Dates of Submission:
May 27, 2003	September 25, 2002 February 12, 2003 May 8, 2003 May 29, 2003

Primary Reviewer:
Michelle Dillahunt — Date: 6/4/03

Team Leader:
Lillie Golson — Date: 6/5/03

cc: ANDA: 76-503
DUP/DIVISION FILE
HFD-613/M Dillahunt/LGolson (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\76503ap.l.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

CHEMISTRY REVIEW(S)

ANDA 76-503

Isotretinoin Capsules, USP, 30 mg

Ranbaxy Laboratories Limited

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-503

2. REVIEW #:1

3. REVIEW DATE: 21-Nov-2002

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-Sept-2002
Acceptable for filing	26-Sept-2002
New Correspondence	21-Oct-2002

7. NAME & ADDRESS OF APPLICANT:

Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon, 122 001
India

US agent: Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Isotretinoin Capsules, USP

9. LEGAL BASIS FOR SUBMISSION:

The ANDA for Isotretinoin Capsules USP 30 mg, is based on the approved suitability petition, Docket #02P-0161/CPI. The subject petition had requested introduction of an intermediate 30 mg strength to the already existing 10, 20 and 40 mg strengths. The approved petition permits this change under section 505 (j)(2)(c) of the federal FD&C act. A copy of the petition approval letter is included in the application. (page 0008)
RLD: Accutane® Capsule 20 mg and 40 mg, NDA 18-662 held by Roche Laboratories, Inc.
Oral use
Paragraph II Patent certification: U.S. patent No. 4464394 expired
Marketing exclusivity
Pediatric marketing exclusivity for U.S. patent No. 4464394 was expired on Feb 7, 2002.
Pediatric marketing exclusivity will be expired on November 2, 2005.
New language for pediatric use, M-12, expiry May 2, 2005.

10. PHARMACOL. CATEGORY:

for the treatment of severe recalcitrant modular acne

11. DOSAGE FORM:
capsules

12. STRENGTH/POTENCY:

30 mg

13. ROUTE OF ADMINISTRATION:
oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

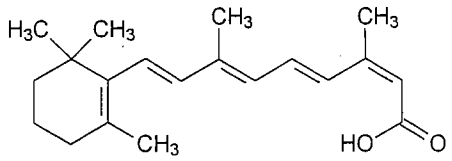
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Isotretinoin. Retinoic acid, 13-*cis*-.$C_{20}H_{28}O_2$. 300.44. 4759-48-2. Keratolytic.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Ranbaxy	Isotretinoin USP	3	adequate	12/5/01	Reviewed by Dr. Shing Liu
	IV	[redacted]	[redacted]	4			
	III	[redacted]	[redacted]	4			
	III	[redacted]	[redacted]	4			
	III	[redacted]	[redacted]	4			
	III	[redacted]	[redacted]	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Isotretinoin capsules, USP, 20 mg	NDA 18-662	Roche Labs (HLR)
Isotretinoin capsules, USP, 40 mg	NDA 18-662	Roche Labs (HLR)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	pending		
Methods Validation	Not required		
Labeling	pending		
Bioequivalence	Acceptable	1/29/03	D. Patel
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-503

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 76-503 is not approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product

Isotrtinoin Capsules USP, 30 mg

Although not a topical drug, it is a dermatological agent. Its primary action is to decrease the production of sebum, which lends itself to the treatment of severe modular and cystic acne.

The product contains a orange-yellow , oily dispersion. It is a soft gelatin capsule with golden yellow opaque body filled with orange-yellow oily dispersion. The capsule is imprinted with "RR" in black ink.

The limit of tretinoin is NMT [redacted]

Isotretinoin is toxic to pregnant women.

Drug substance

It is a yellow or light orange, crystalline powder. Differs from tretinoin (vitamine A) only in the configuration of the unsaturation at the α and β carbon atoms, which is cis rather than trans.

The drug substance is practically insoluble in water, soluble in chloroform, sparingly soluble in alcohol, isopropyl alcohol and ethylene glycol 400.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used for the treatment of severe modular and cystic acne..

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to the deficiencies found in the following areas.

(1) [redacted]

III. Administrative

A. Reviewer's Signature

Liang-Lii Huang, Ph.D.

B. Endorsement Block

Liang-Lii Huang, Ph.D./11/27/02 L Huang 1/31/03
James Fan, Team Leader/11/25/02
Sarah Ho, Project Manager/11/25/02

C. CC Block

ANDA 76-503
ANDA DUP 76-503
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Redacted 18

Page(s) of trade secret and /or confidential commercial information

ANDA 76-503

Isotretinoin Capsules, USP, 30 mg

Ranbaxy Laboratories Limited

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review Data Sheet

1. ANDA 76-503

2. REVIEW #:2

3. REVIEW DATE:
05-May-2003

APPEARS THIS WAY
ON ORIGINAL

4. REVIEWER:
Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-Sept-2002
Acceptable for filing	26-Sept-2002
New Correspondence	21-Oct-2002
Minor amendment	24-Feb-2003

7. NAME & ADDRESS OF APPLICANT:

Ranbaxy Laboratories Limited
Sector 18, Udyog Vihar Industrial Area
Gurgaon, 122 001
India

US agent: Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sotret ™
b) Non-Proprietary Name (USAN):
Isotretinoin Capsules, USP

9. LEGAL BASIS FOR SUBMISSION:

The ANDA for Isotretinoin Capsules USP 30 mg, is based on the approved suitability petition, Docket #02P-0161/CPI. The subject petition had requested introduction of an intermediate 30 mg strength to the already existing 10, 20 and 40 mg strengths. The approved petition permits this change under section 505 (j)(2)(c) of the federal FD&C act. A copy of the petition approval letter is included in the application. (page 0008)
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Marketing exclusivity
Pediatric marketing exclusivity for U.S. patent No. 4464394 was expired on Feb 7, 2002.
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for the treatment of severe recalcitrant modular acne

11. DOSAGE FORM:

capsules

12. STRENGTH/POTENCY:

30 mg

13. ROUTE OF ADMINISTRATION:

oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

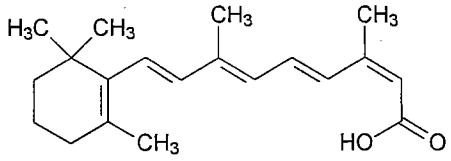
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Isotretinoin. Retinoic acid, 13-*cis*-.$C_{20}H_{28}O_2$. 300.44. 4759-48-2. Keratolytic.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	Ranbaxy	Isotretinoin USP	1	adequate	5/15/03	Reviewed by Dr. L. Huang
[redacted]	IV	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			

APPEARS THIS WAY ON ORIGINAL

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Isotretinoin capsules, USP, 20 mg	NDA 18-662	Roche Labs (HLR)
Isotretinoin capsules, USP, 40 mg	NDA 18-662	Roche Labs (HLR)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6/3/2003	
Methods Validation	Not required		
Labeling	Acceptable	6/5/03	M. Dillahunt
Bioequivalence	Acceptable	1/29/03	D. Patel
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-503

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 76-503 is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product

Isotretinoin Capsules USP, 30 mg

Although not a topical drug, it is a dermatological agent. Its primary action is to decrease the production of sebum, which lends itself to the treatment of severe modular and cystic acne.

The product contains a orange-yellow , oily dispersion. It is a soft gelatin capsule with golden yellow opaque body filled with orange-yellow oily dispersion. The capsule is imprinted with "RR" in black ink.

The limit of tretinoin is NMT ——

Isotretinoin is toxic to pregnant women.

Drug substance

It is a yellow or light orange, crystalline powder. Differs from tretinoin (vitamin A) only in the configuration of the unsaturation at the α and β carbon atoms, which is cis rather than trans.

The drug substance is practically insoluble in water, soluble in chloroform, sparingly soluble in alcohol, isopropyl alcohol and ethylene glycol 400.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used for the treatment of severe modular and cystic acne.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

III. Administrative

A. Reviewer's Signature

Liang-Lii Huang, Ph.D.

B. Endorsement Block

Liang-Lii Huang, Ph.D./5/22/03 L. Huang 6/6/03
James Fan, Team Leader/5/22/03

C. CC Block

ANDA 76-503
ANDA DUP 76-503
DIV FILE
Field Copy

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APPEARS THIS WAY
ON ORIGINAL

Redacted 15

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

BIOEQUIVALENCE REVIEW(S)

JAN 29 2003

Isotretinoin Capsules USP
30 mg
ANDA 76-503
Reviewer: Devvrat Patel
V:\FirmsNZ\Ranbaxy\LTRS&REV\76503N0902.doc

Ranbaxy Laboratories Limited
Gurgaon, India
Submission Date:
September 25, 2002

REVIEW OF BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

Introduction

First Generic: Isotretinoin 10 mg, 20 mg 40 mg capsules have been approved previously. Isotretinoin 30 mg is a new strength and there is no corresponding innovator strength.

Indication: Isotretinoin is indicated for the treatment of severe recalcitrant acne.

Recommended dose: The recommended dosage range is 0.5 to 1 mg/kg/day given with food in two divided doses for 15 to 20 weeks.

RLD: Accutane® 40 mg capsules, manufactured by Hoffman-La Roche (NDA 18662, May 7, 1982).

Contents of Submission:

- Single-dose, 2-way crossover, fasting bioequivalence study on 40 mg capsules
- Single-dose , 3-way crossover, fed and fasting bioequivalence study on 40 mg capsules
- Waiver request for 30 mg capsule
- A 3-way comparative in vitro dissolution data for isotretinoin 30 mg, 40 mg, and Accutane® 40 mg capsules

Drug Information

Isotretinoin is a retinoid, which inhibits sebaceous gland function and keratinization. Oral absorption of isotretinoin is optimal when taken with food or milk. The oral absorption of isotretinoin is consistent with first-order kinetics and can be described with a linear two-compartment model. Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

After oral administration of isotretinoin, 4- *oxo* -isotretinoin is the major metabolite identified in the blood. Both parent compound and metabolites are further metabolized into conjugates, which are excreted. The terminal elimination half-life of isotretinoin ranges from 10 to 20 hours. The mean elimination half-life of 4- *oxo* -isotretinoin is 25 hours (range 17 to 50 hours). After both single and multiple doses, the accumulation ratio of 4- *oxo* -isotretinoin to parent compound is 3 to 3.5.

Background

This ANDA is based on the approved suitability petition, Docket No. 02P-0161/CP1 (August 8, 2002). The petition had requested introduction of an intermediate 30 mg strength to the already existing 10 mg, 20 mg and 40 mg strengths. The reference listed drug product to which the firm referred in the petition is Accutane® 40 mg capsules. The petition was approved based on the fact that the change in strength for the drug does not pose questions of safety or effectiveness because the 30 mg strength is an intermediate dosage strength and the drug product is prescribed based upon a mg/kg basis.

Since 30 mg is a new strength and there is no corresponding strength available for the innovator product, this ANDA is supported with the bioavailability/bioequivalence study conducted on the 40 mg strength capsules. The firm claims that the composition of isotretinoin 30 mg is proportionally similar to the 40 mg strength. Based on this information, the firm is requesting a waiver of the requirement to demonstrate *in vivo* bioequivalence for the 30 mg strength in accordance with 21 CFR 320.22(d)(2).

The bioavailability/bioequivalence studies were conducted on isotretinoin 40 mg capsules and Accutane® 40 mg capsules. These studies are the same as submitted in another Ranbaxy ANDA (76-041, November 30, 2000) for isotretinoin 10 mg, 20 mg and 40 mg capsules. The firm claims that that acceptability of cross-referencing bioequivalence studies was discussed and agreed upon with the Agency.

History

Isotretinoin 10 mg, 20 mg and 40 mg capsules (ANDA 76-041, November 30, 2000)
The fasting and nonfasting studies on 40 mg capsules were found to be acceptable by the DBE. Following deficiencies were found in the submission:

1. The dissolution testing was found unacceptable. Since there is no USP method listed for dissolution testing of isotretinoin capsules, the firm was informed to develop another dissolution testing method based on the Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045, and the guidance document: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997.
2. According to the test of "Dilution Integrity", the samples were diluted with buffer. The firm was informed that samples should be diluted with blank plasma for the future studies.
3. The DBE requested single-dose fasting bioequivalence study on isotretinoin 20 mg capsules, and the firm may request a waiver for the 10 mg strength.

ANDA 76-041 Amendment (September 21, 2001)
Following were the responses to the deficiencies:

1. The firm used [redacted] as the dissolution media, and essentially used the method that was submitted in the original ANDA. The method in the amendment was

not acceptable. The DBE requested submission of dissolution data using [redacted] as the medium, and the [redacted] with an optimum rotation speed (not to exceed [redacted], and the sampling times of 20, 40, 60, 90, and 120 minutes.

2. The firm acknowledged that the samples should be diluted with blank plasma for the future studies.
3. The single-dose fasting study on 20 mg strength capsule was found to be incomplete; the DBE requested the assayed potency data for the RLD, Accutane® 20 mg capsule.

ANDA 76-041 Amendment (December 4, 2001)
Responses and deficiencies:

1. The firm submitted the assayed potency data; the single-dose fasting study on 20 mg capsule was found to be acceptable.
2. The DBE made additional recommendations regarding the dissolution methodology.

ANDA 76-041 Amendment (February 4, 2002)
The DBE accepted the biostudies on isotretinoin 40 mg and 20 mg capsules, and granted a waiver on 10 mg capsules. The DBE also accepted the comparative dissolution testing on the 40 mg, 20 mg and 10 mg capsules. The DBE accepted the following dissolution method for isotretinoin capsules:

Medium: [redacted]
Volume: [redacted]
Apparatus: [redacted]
RPM: [redacted]
Specifications: Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes (interim).

<u>Bioequivalence Studies</u> (Current submission)

1. Protocol 001182: Comparative, randomized, single-dose, 2-way crossover bioavailability study of Ranbaxy and Roche Labs (Accutane®) 40 mg isotretinoin soft gelatin capsules in healthy adult males following administration of 80 mg dose under fasting conditions.

2. Protocol 001183: Comparative, randomized, single-dose, 3-way crossover bioavailability study of Ranbaxy and Roche Labs (Accutane®) 40 mg isotretinoin soft gelatin capsules in healthy adult males following administration of 80 mg dose under fed and fasting conditions.

Comments

The DBE found both studies to be acceptable as shown in the review for ANDA 76-041 submitted on November 30, 2000.

Formulation Comparison

A quantitative comparison between the 10 mg, 20 mg and 40 mg capsules in ANDA 76-041 and isotretinoin 30 mg capsules (this ANDA) is shown in Table 1.

Table 1: Formulation comparison

Ingredient	STRENGTHS SUBMITTED IN ANDA 76-041						THIS ANDA	
	10 mg	% w/w	20 mg	% w/w	40 mg	% w/w	30 mg	% w/w
Isotretinoin USP *	10.30#	6.44	20.60#	6.44	41.20#	13.19##	30.90#	9.66##
Hydrogenated Soybean Oil								
Hydrogenated Vegetable Oil NF								
White Wax NF								
Edetate Disodium USP								
Butylated Hydroxyanisole NF								
Soybean Oil USP **								
Total								
Gelatin NF								
Glycerin USP								
Ferric Oxide Red NF								
FD&C Blue No. 1								
FD&C Red No. 3								
D&C Yellow No. 10								
FD&C Yellow No. 6								
Titanium Dioxide USP								
Methylparaben NF								
Propylparaben NF								

* Quantity based on [redacted] assay on [redacted]

\# Contains [redacted]

[redacted]

Comments

The compositions of isotretinoin 30 mg and 40 mg capsules are proportionally similar.

Dissolution Testing

The firm conducted the dissolution testing using a method that was accepted by the DBE (ANDA 76-041 Amendment, February 4, 2002). The method and results are shown in Table 2.

The firm has submitted a three way comparative in vitro dissolution data for isotretinoin 30 mg capsules, isotretinoin 40 mg capsules, and Accutane® 40 mg capsules. The dissolution data for the isotretinoin 40 mg capsule, and Accutane 40 mg capsule are reproduced from the ANDA 76-041.

Table 2:

Method:	**DBE recommended method in ANDA 76-041**
Analyte:	Isotretinoin
Dosage Form and Strengths:	Soft Gelatin Capsules 30 mg and 40 mg
No. of Units Tested:	12 Capsules
Medium:	
Volume:	
Apparatus:	
RPM:	
Specifications:	NLT — (Q) of the labeled amount of isotretinoin is dissolved in 90 minutes

Mean Dissolution Data

Isotretinoin Capsules **Lot No. 1161265** **Strength: 30 mg** **Expiration Date: 9/2003** **No. of Units: 12**					**Isotretinoin Capsules** **Lot No. 1077652** **Strength: 40** **Expiration Date: 5/2002** **No. of Units: 12**				**Accutane® Capsules** **Lot No. U0588** **Strength: 40 mg** **Expiration Date: 10/2002** **No. of Units: 12**			
% Dissolved					% Dissolved				% Dissolved			
Time (min)	Mean	Min	Max	% CV	Mean	Min	Max	% CV	Mean	Min	Max	% CV
20	17	—	—	27.3	20	—	—	44.0	30	—	—	25.0
40	39	—	—	19.9	44	—	—	20.9	53	—	—	16.8
60	73	—	—	10.8	70	—	—	10.9	72	—	—	11.0
90	87	—	—	10.3	85	—	—	8.2	88	—	—	6.5
120	98	—	—	5.6	93	—	—	6.6	94	—	—	7.3

F_2 Calculations:

Accutane® 40 mg vs. isotretinoin 40 mg:	59.95
Accutane® 40 mg vs. isotretinoin 30 mg:	52.75
Isotretinoin 40 mg vs. isotretinoin 30 mg:	70.31

Comments

The firm has conducted the dissolution testing using the same method as recommended by the DBE. The test product meets the dissolution specifications (NLT [redacted] dissolved in 90 minutes).

Isotretinoin 40 mg and 30 mg capsules have similar dissolution profile. The dissolution testing submitted by the firm is acceptable.

Waiver request

A waiver of *in vivo* bioequivalence study requirements for the isotretinoin 30 mg capsules may be granted based on the following:

1. The DBE has accepted the Ranbaxy's bioequivalence studies on isotretinoin 20 mg and 40 mg and are deemed bioequivalent to their respective RLD product strengths (ANDA 76-041).

2. The DBE has accepted the firm's dissolution method and has approved the comparative dissolution testing conducted on 10 mg, 20 mg, and 40 mg capsules. Based on the proportionally similar formulation to 20 mg capsule, isotretinoin 10 mg capsule was granted a waiver for the biostudy requirement.

3. The *in vitro* dissolution profile for isotretinoin 30 mg capsule is comparable to that of isotretinoin 40 mg capsule.

4. The compositions of isotretinoin 30 mg and 40 mg capsules are proportionally similar. The inactive ingredients in formulations of 30 mg and 40 mg capsules are identical, except for the [redacted]

Recommendations

The dissolution testing conducted by the firm on its isotretinoin 30 mg and 40 mg capsules are acceptable. The formulation for the 30 mg capsule is proportionally similar to the 40 mg capsule, which underwent bioequivalency testing. A waiver of *in vivo* bioequivalence study requirements for isotretinoin 30 mg capsule is granted.

Devvrat Patel

Devvrat Patel, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 1/27/2003

Concur: _____ Date 1/29/03
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

CC: ANDA 76503
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76503 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Isotretinoin Capsule 30 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted]. The test product should meet the following specifications:

Not less than [redacted] Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76503
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

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Printed in final on January 27, 2003

1/27/03

Endorsements: (Final with Dates)
HFD-655/ Patel 1/27/2003
HFD-655/ Nerurkar
HFD-650/ D. Conner 1/29/03

BIOEQUIVALENCY - ACCEPTABLE

Submission date:
September 25, 2002

1. **DISSOLUTION WAIVER** (DIW)

Strengths: 30 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

3

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-503 SPONSOR : Ranbaxy Laboratories

DRUG AND DOSAGE FORM : Isotretinoin Capsule

STRENGTH(S) : 30 mg

TYPES OF STUDIES : Fasting and fed studies on 40 mg capsules (reproduced from ANDA 76-041)

CLINICAL STUDY SITE(S) : [redacted]

ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : Fasting and fed studies on 40 mg capsules are acceptable (ANDA 76-041).

DISSOLUTION : The dissolution testing is acceptable. The dissolution testing should be conducted in [redacted], using [redacted]. The test product should meet the following specifications: NLT [redacted]Q) of isotretinoin is dissolved in 90 minutes. A waiver of *in vivo* bioequivalence study requirements for 30 mg strength capsule is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Devvrat Patel, Pharm.D. BRANCH : II

INITIAL : Devvrat Patel DATE : 1-27-2003

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : [signature] DATE : 1/27/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] DATE : 1/29/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : October 3, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 03-OCT-2002

SUBJECT: Examination of the bioequivalence dissolution and request for waiver submitted with an ANDA for Isotretinoin Capsules USP, 30 mg **(per suitability petition Docket No. 02p-0161/CP1 approved August 8, 2002)** to determine if the application is substantially complete for filing.

Ranbaxy Laboratories Ltd. has submitted ANDA 76-503 for Isotretinoin Capsules USP, 30 mg. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence dissolution and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for studies and request for dissolution and waiver submitted by Ranbaxy on September 25, 2002 for its Isotretinoin product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-503

CORRESPONDENCE

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

N/AF

May 29, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Michelle Dillahunt, Labeling

UPS & FAX

LABELING COMMITMENT
TO PENDING APPLICATION

RE: Isotretinoin Capsules USP, 30 mg
ANDA 76-503

Dear Madam,

Reference is made to the pending ANDA 76-503 for Isotretinoin Capsules, USP, 30 mg submitted on September 25, 2002 and telephone contact with Ms. Michelle Dillahunt, OGD, May 28, 2003.

By the referenced phone conversations above, Ms. Dillahunt has made Ranbaxy aware of the following requested changes to the labeling for Sotret™ Isotretinoin Capsules, 30 mg.

> ***Please revise your storage statement to the following*** **"Store at 20 - 25°C (68 - 77° F); [see USP Controlled Room Temperature]."**

As indicated as acceptable by Ms. Dillahunt on May 28, 2003, Ranbaxy Laboratories Limited commits to make this change in accordance with Office of Generic Drugs recommendations, at the time of our next printing. Ranbaxy Laboratories Limited commits to providing the Office of Generic Drugs copies of all labeling reflecting these changes as appropriate in the Annual Report.

If you have any additional questions, please call me at 609-720-5336 or Abha Pant at 609-720-5666.

Sincerely,

Anthony M. Maffia, III
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAY 30 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT
N/AF

May 8, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Michelle Dillahunt, Labeling

UPS

LABELING
ADDITIONAL INFORMATION

RE: Isotretinoin Capsules USP, 30 mg
ANDA 76-503

Dear Madam,

Reference is made to the pending ANDA 76-503 for Isotretinoin Capsules, USP, 30 mg submitted on September 25, 2002 and telephone contact from Ms. Michelle Dillahunt, Office of Generic Drugs, May 8, 2003.

As per Ms. Dillahunt's request Ranbaxy is providing twelve copies of the following pieces of labeling, removed from the spiral bound brochures, in unbound fashion to assist in the review process:

Attachment 1	Letter of Understanding for Prescribers
Attachment 2	Isotretinoin Survey form (from brochure for female patients)
Attachment 3	Isotretinoin Survey form (from prescription blister card)
Attachment 4	Patient Information/Consent (for female patients concerning birth defects)
Attachment 5	Informed Consent/Patient Agreement (for all patients)
Attachment 6	Patient qualification checklist form
Attachment 7	*Always Careful, Always Ready* video script (This was provided in Labeling Amendment of February 12, 2003, Attachment 3, pages 142A-142E. We have provided it here again for ready reference. The same video that is in use for approved ANDA 76-041 will be provided for physician use for ANDA 76-503.)

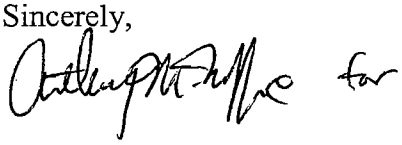
Ranbaxy received approval for ANDA 76-041, Isotretinoin Capsules, USP, 10 mg, 20 mg & 40 mg on December 24, 2002. Please note that other than the use of "30 mg" in the labeling where appropriate, the labeling for this application will follow that of ANDA 76-041 and share the same elements of Ranbaxy's *I.M.P.A.R.T* Risk Management Program.

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

ANDA 76-503
Labeling Amendment
May 8, 2003

If you have any additional questions, please call me at 609-720-5336 or Abha Pant at 609-720-5666.

Sincerely,



Anthony M. Maffia, III (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

APPEARS THIS WAY
ON ORIGINAL

RANBAXY
PHARMACEUTICALS INC.

February 24, 2003

Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX
MINOR
AMENDEMENT

ORIG AMENDMENT
N/AM

Reference: **Isotretinoin Capsules, USP, 30 mg**
ANDA 76-503

Dear Sir/Madam:

Reference is made to our pending ANDA 76-503 for Isotretinoin Capsules, USP, 30 mg submitted to the Agency on September 25, 2002.

Reference is also made to the Minor Amendment fax received February 4, 2003.

The deficiency questions and responses are addressed on the following pages, following the order in the original letter.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this amendment has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact Anthony M. Maffia at 609-720-5336, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment.

Sincerely,

Anthony M. Maffia, III
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
FEB 25 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIGINAL

February 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Michelle Dillahunt, Labeling

UPS

LABELING AMENDMENT
TO PENDING APPLICATION

ORIG AMENDMENT
N/AF

FPL

RE: Isotretinoin Capsules USP, 30 mg
ANDA 76-503

Dear Madam,

Reference is made to the pending ANDA 76-503 for Isotretinoin Capsules, USP, 30 mg submitted on September 25, 2002.

Ranbaxy received approval for ANDA 76-041, Isotretinoin Capsules, USP, 10 mg, 20 mg & 40 mg on December 24, 2002. We are submitting this Labeling Amendment to ANDA 76-503, Isotretinoin Capsules, USP, 30 mg, as per telephone conversations with Ms. Michelle Dillahunt of OGD, in order to incorporate all the appropriate changes from the approved application. Other than the use of "30 mg" in the labeling where appropriate, the labeling for this application will follow that of ANDA 76-041 and share the same elements of Ranbaxy's *I.M.P.A.R.T* Risk Management Program.

Copies of the following relevant OGD Correspondence, from ANDA 76-041, Isotretinoin Capsules, USP, 10 mg, 20 mg & 40 mg may be found in **Attachment 1**:

1. Pharmacy Compliance Survey comments email September 27, 2002
2. Pharmacy Dispensing Guide Content facsimile received November 6, 2002
3. Final labeling comments for ANDA 76-041 and Ranbaxy's response dated November 11, 2002
4. Letter from Ranbaxy to the Agency dated December 16, 2002 in which Ranbaxy committed to making final changes to labeling for ANDA 76-041 before commercialization as indicated by telephone contact with Ms. Michelle Dillahunt, OGD
5. Approval Letter for ANDA 76-041, Isotretinoin Capsules, USP, 10 mg, 20 mg & 40 mg, December 24, 2002

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600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

ANDA 76-503
Labeling Amendment
February 11, 2003

To facilitate review we have provided a side-by-side labeling comparison with Ranbaxy's revised labeling and the previously submitted labeling, with all differences explained and shown with the use of color, in **Attachment 2.** We have provided a copy of our educational video script with the revised title, *Always Careful, Always Ready,* in **Attachment 3**. The same video that is in use for approved ANDA 76-041 will be provided for physician use for ANDA 76-503.

Reference is made to the teleconference which took place on October 25, 2002 between The Office of Generic Drugs, Division of Medical Safety, Ranbaxy and IMS regarding our Pharmacy Compliance Survey Proposal. A copy of the revised proposal with changes based on that conversation is included in **Attachment 4**. This proposal is a copy of that which was approved in conjunction with ANDA 76-041.

Twelve sets of the final printed labeling are included in the **"original"** copy of this response and an additional 6 sets of the final printed labeling are provided in the duplicate copy. These may be found in **Attachment 5**.

Please note, based on conversation with and comments from the Agency, Ranbaxy's previously submitted risk management program name, *Isotretinoin Medication Program Alerting Risks of Teratogenicity* has been replaced with *Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity.* The I.M.P.A.R.T. acronym remains unchanged. This change in name is reflected throughout all the components of labeling in this amendment and mirrors that of approved ANDA 76-041.

If you have any additional questions, please call me at 609-720-5336 or Abha Pant at 609-720-5666.

Sincerely,

Anthony M. Maffia, III (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

October 21, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

ADDITIONAL INFORMATION

NEW CORRESP
NC

RE: Isotretinoin Capsules USP, 30 mg
ANDA 76-503

Dear Sir/Madam:

Reference is made to the pending ANDA 76-503 for Isotretinoin Capsules, USP, 30 mg submitted on September 25, 2002.

Please find a revised page for page 4274. The Permeation Test Results data submitted for the simulated bulk transfer pack was submitted incorrectly. We are hereby submitting the correct data. This revised page is found in **Attachment 1**.

Please find a revised page for page 4370. The dissolution and uniformity data table submitted on this page of the original ANDA is missing crucial data. We are hereby submitting the revised page with complete data making it consistent with the data presented throughout the remaining application. This revised page is found in **Attachment 2.**

Lastly, we would like to clarify the packaging of —ottles during exhibit batch packaging shown in the executed batch records. While this container configuration was packaged at the time of exhibit batch, Ranbaxy will not package or market this configuration for commercial use. Only 10's blisters, enclosed in the prescription blister card presenting all the information, cautions and warnings associated with the I.M.P.A.R.T. Risk Management Program will be packaged and distributed commercially.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Office of Generic Drugs/International Operation Group.

If you have any additional questions, please call me at 609-720-5336 or Abha Pant at 609-720-5666.

Sincerely,

Anthony M. Maffia, III (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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OCT 22 2002
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ANDA 76-503

OCT 30 2002

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Isotretinoin Capsules USP, 30 mg

DATE OF APPLICATION: September 25, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 26, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Ho
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research