

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

76-041

Trade Name: Sotret Capsules
10mg, 20mg, and 40mg

Generic Name: Isotretinoin Capsules USP

Sponsor: Ranbaxy Pharmaceuticals, Inc.

Approval Date: December 24, 2002

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APPLICATION NUMBER:

76-041

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

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APPROVAL LETTER

ANDA 76-041

DEC 24 2002

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 November 30, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Sotret™ Capsules (Isotretinoin Capsules USP), 10 mg, 20 mg, and 40 mg.

Reference is also made to your amendments dated September 21, December 4, December 11, and December 20, 2001; and April 1, May 3, July 15, August 5, August 9, November 11, and December 2, 2002.

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 (BCPA), 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. The Division of Bioequivalence has determined your Sotret™ Capsules, 10 mg, 20 mg, and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Accutane® Capsules, 10 mg, 20 mg, and 40 mg, respectively, of HLR Technology). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

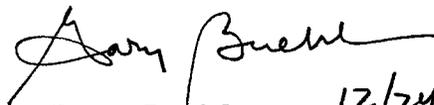
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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 that 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 proposed or 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,



Gary Buehler 12/24/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-041

FINAL PRINTED LABELING

SOTRET™
ISOTRETINOIN CAPSULES, USP
Rx only

CAUSES BIRTH DEFECTS



50222880

DO NOT GET PREGNANT

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

Major human fetal abnormalities related to Sotret 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, microplina, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphism; 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.

Sotret is 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 Sotret therapy and understand behaviors associated with an increased risk of pregnancy.
- **Must** be reliable in understanding and carrying out instructions.

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

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

- 1) Read the booklet entitled *Isotretinoin Medication Program: Alerting you to the 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 Sotret
- 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 Sotret therapy and for 1 month after stopping Sotret. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Sotret 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 Sotret treatment course, the I.M.P.A.R.T. procedures for Sotret, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Sotret Qualification Stickers
- 3) To use the yellow self-adhesive Sotret Qualification Sticker: Sotret should not be prescribed or dispensed to any patient (male or female) without a yellow self-adhesive Sotret Qualification Sticker.

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

- **Must** have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Sotret prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Sotret. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Sotret 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 Sotret 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 Sotret therapy, during Sotret therapy, and for 1 month after discontinuing Sotret 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 Sotret. 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

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 \pm 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: Sotret is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Sotret should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Sotret is indicated only for those females who are not pregnant, because Sotret 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: Sotret is contraindicated in patients who are hypersensitive to this medication or to any of its components. Sotret 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: Sotret may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Discontinuation of Sotret 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 Sotret*.

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 Sotret 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. Sotret 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 Sotret is given and then at intervals until the lipid response to Sotret 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 Sotret therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Sotret therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS: *Laboratory Tests*).

The cardiovascular consequences of hypertriglyceridemia associated with Sotret 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 Sotret 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 Sotret, 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 Sotret immediately (see ADVERSE REACTIONS: *Gastrointestinal*).

Skeletal: Bone Mineral Density: Effects of multiple courses of Sotret on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy

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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, Hypertosis, and Premature Epiphyseal Closure*).

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Skeletal: Bone Mineral Density: Effects of multiple courses of Sotret on the developing musculoskeletal system are unknown. There is some evidence that long-term high-dose treatment

Information Concerning Your Treatment with Sotret™ (isotretinoin). All patients should sign the Informed Consent/Patient Agreement.

- Females of childbearing potential should be instructed that they must not be pregnant when Sotret therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Sotret, while taking Sotret, and for 1 month after Sotret has been stopped. They should also sign a consent form prior to beginning Sotret therapy. They should be given an opportunity to enroll in the Isotretinoin 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 Sotret prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).

- Sotret is found in the semen of male patients taking Sotret, 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 Sotret therapy is appropriate in this setting (see WARNINGS: *Psychiatric*).

- Patients should be informed that they must not share Sotret 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 discontinuation of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Sotret.

- Patients should be reminded to take Sotret 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 Sotret 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 Sotret. Consideration should be given to discontinuation of Sotret if any significant abnormality is found.

- Neutropenia and rare cases of agranulocytosis have been reported. Sotret 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 Sotret to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.

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

- Micro-dosed Progesterone Preparations:** Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Sotret therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy with these 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 Sotret. 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 Sotret. 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 Sotret. 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:

- **Must** be 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 Sotret Survey and have been given the opportunity to enroll (see PRECAUTIONS).

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

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

Patient Type	Pregnancy Test Required	Qualification Date	Sotret 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 Sotret, 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 Program to Prevent Pregnancy Specialist will be available to discuss Ranbaxy pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

Sotret 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 Sotret Qualification Stickers. Sotret should not be prescribed or dispensed without a yellow self-adhesive Sotret Qualification Sticker.

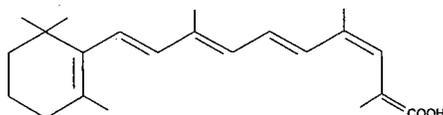
INFORMATION FOR PHARMACISTS:

SOTRET MUST ONLY BE DISPENSED:

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

DESCRIPTION: Isotretinoin, a retinoid, is available as Sotret in 10-mg, 20-mg and 40-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 systems: 10 mg - iron oxide (red) and titanium dioxide; 20 mg - FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg - FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

Chemically, isotretinoin acid 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 Sotret, 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, Sotret 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-∞} (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*-

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 Sotret has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Sotret 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 Sotret 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 Sotret on epiphyseal closure is unknown.

Vision Impairment: Visual problems should be carefully monitored. All Sotret patients experiencing visual difficulties should discontinue Sotret 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 Sotret Pregnancy Prevention and Risk Management Programs consist of the *Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity* (I.M.P.A.R.T.) and the *Sotret Program to Prevent Pregnancy* (PPP). I.M.P.A.R.T. should be followed for prescribing Sotret with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) reading the booklet entitled *Isotretinoin Medication Program: Alerting you to the 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 Sotret 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: Sotret 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 Sotret prescription.
 - 2) The I.M.P.A.R.T. *Letter of Understanding* attests that Sotret prescribers understand that Sotret 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 Sotret and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.
- The Prescriber Checklist attests that Sotret prescribers know the risk and severity of injury/birth defects from Sotret; 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 Sotret treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and use of qualified prescriptions with the yellow self-adhesive Sotret Qualification Sticker.
- 3) The yellow self-adhesive Sotret 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) Sotret Program to Prevent Pregnancy (PPP) is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The PPP includes information on the risks and benefits of Sotret which is linked to the Sotret Medication Guide dispensed by pharmacists with each prescription.

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

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

The booklet for female patients, *Be Clever, Be Cautious, Be Certain, Sotret Program to Prevent Pregnancy 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 Survey; and a qualification checklist affirming the conditions under which female patients may receive Sotret. 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 Sotret on bone loss is not established, physicians should use caution when prescribing Sotret 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 spondylolysis and 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 capsules while involved in these activities. While causality to Sotret has not been established, an effect cannot be ruled out.

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Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolysis 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 capsules while involved in these activities. While causality to Sotret has not been established, an effect cannot be ruled out.

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 Sotret 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 Sotret 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 Sotret.

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

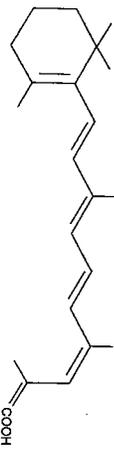
Cardiovascular: palpitation, tachycardia, vascular thrombotic disease, stroke

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

DESCRIPTION: Isotretinoin, a retinoid, is available as Sorrel in 10-mg, 20-mg and 40-mg soft gelatin capsules for oral administration. Each capsule contains butylated hydroxyanisole, edentate 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 systems: 10 mg - iron oxide (red) and titanium dioxide; 20 mg - FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg - FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

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



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

Modular Acne: Clinical improvement in nodular acne patients occurs in association with a reduction in sebaceous secretion. The decrease in sebaceous secretion is temporary and is related to the dose and duration of treatment with Sorrel, 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, Sorrel 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

Isotretinoin capsules 2 x 40 mg Capsules	Mean (%CV), N=74			
	AUC _{0-∞} (ng·hr/mL)	C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)
Fed ¹	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (50%)

¹Eating 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 (retinol), and 4-*oxo*-retinoic acid (4-*oxo*-retinol). 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 reversibly oxidized to 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-retinol.

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

2) The I.M.D.A.R.T. Letter of Understanding assesses that Sorrel prescribers understand that Sorrel is a retinogen, have read the I.M.D.A.R.T. Guide to Best Practices, understand their responsibilities in pre-defined in the boxed CONTRAINDICATIONS AND WARNINGS.

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

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

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

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

The booklet for female patients, *Be Clever, Be Cautious, Be Certain, Sorrel Program to Prevent Pregnancy and Risk Management Program for Women*, also includes a referral program that offers females free contraceptive 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 Survey, and a qualification checklist affirming the conditions under which female patients may receive Sorrel. 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 contraceptive counseling line, and a video about the most common reasons for unplanned pregnancies.

General: Although an effect of Sorrel on bone loss is not established, physicians should use caution when prescribing Sorrel 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 anticonvulsants.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of sprain/dislocation 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 capsules while involved in these activities. While causality to Sorrel 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 Sorrel 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*

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% based on unadjusted patients (92% did not have significant decreases or had increases (adjusted for body mass index). Nine one (10.6%) patients had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty (9.9%) 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 reportable 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 hypertiglyceridemia 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: hypertiglyceridemia (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, hiccups, 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.

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

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

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

My prescriber has answered all my questions about Sotret and I understand that it is my responsibility to get pregnant during Sotret treatment or for 1 month after I stop taking Sotret.

Initial: _____ Date: _____
 I now authorize my prescriber _____ to begin my treatment with Sotret.
 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 Sotret 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 Sotret if there is anything that you do not understand about all the information you have received about using Sotret.

1. I, _____ (Patient's Name) understand that Sotret 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 Sotret. 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 interest in activities, and thoughts of suicide. Initials: _____

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, tendinitis, 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 luminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas, 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 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 urogenital 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 LD₅₀ 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.

Sotret 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 educational counseling as described in the boxed CONTRAINDICATIONS AND WARNINGS. Contraceptives 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.

DOSE AND ADMINISTRATION: Sotret should be administered with a meal (see PRECAUTIONS: *Information for Patients and Prescribers*).

The recommended dosage range for Sotret is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.5, 1.0, and 2.0 mg/kg/day, 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 Sotret with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food intake instructions.

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

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

All patients should read the rest of this Medication Guide.

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

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

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

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

Who should not take Sotret?
Do not take Sotret if you are pregnant, plan to become pregnant, or become pregnant during treatment. Sotret causes severe birth defects. All females should read the section "Who should not take Sotret?" for more information and warnings about pregnancy.

Important warnings for females taking Sotret? For more information and warnings about pregnancy, see the instructions in this Medication Guide.

Do not take Sotret unless you completely understand its possible risks and are willing to follow the instructions in this Medication Guide.

Tell your prescriber if you or someone in your family has had any kind of mental problems, including depression, diabetes, osteoporosis (bone loss), weak bones, anorexia nervosa, or a disorder where people eat too little, or any other important health problems. Tell your prescriber if you have had any food or drug allergies you have had in the past. These problems do not necessarily mean you cannot take Sotret, but your prescriber needs this information to discuss if Sotret is right for you. Do not take Sotret if you are pregnant, plan to become pregnant, or become pregnant during treatment. Sotret causes severe birth defects. All females should read the section "Who should not take Sotret?" for more information and warnings about pregnancy.

How should I take Sotret?
You will get no more than a 30-day supply of Sotret at a time, to be sure you check your Sotret each month to discuss side effects.

Your prescription should have a special yellow self-adhesive sticker attached to it. If you have a prescription that does not have this yellow self-adhesive sticker, call your pharmacist to get a new prescription unless it has the yellow self-adhesive sticker.

The amount of Sotret you take has been specially chosen for you and may change during your treatment.

You will take Sotret 2 times a day with a meal, unless your prescriber tells you otherwise. You should take Sotret with a full glass of liquid. This will help prevent the medication inside the stomach from irritating the lining of your esophagus (connection between mouth and stomach). If you have trouble swallowing, do not chew or suck on the capsule.

If you miss a dose, just skip that dose. Do not take 2 doses the next time.

You should return to your prescriber as directed to make sure you don't have signs of side effects. Because some of Sotret's serious side effects show up in blood tests, some of which may involve blood tests (monthly visits for female patients should include a urine pregnancy test).

What should I avoid while taking Sotret?
Do not get pregnant while taking Sotret. See "What is the most important information I should know about Sotret?" for more information.

Do not get pregnant while taking Sotret. See "What is the most important information I should know about Sotret?" for more information.

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

Body Weight	0.5 mg/kg	1 mg/kg	2 mg/kg*
kilograms			
pounds			
40	88	20	40
50	110	25	50
60	132	30	60
70	154	35	70
80	176	40	80
90	198	45	90
100	220	50	100

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

Information for Pharmacists: Sorret must only be dispensed in no more than a 30-day supply and only on presentation of a Sorret prescription with a yellow self-adhesive Sorret Qualification Sticker written within the previous 7 days. **REFILLS REQUIRE A NEW WRITTEN PRESCRIPTION WITH A YELLOW SELF-ADHESIVE SORRET QUALIFICATION STICKER WITHIN THE PREVIOUS 7 DAYS.** No telephone or computerized prescriptions are permitted.

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

HOW SUPPLIED: Soft gelatin capsules, 10 mg (light pink), imprinted "SR". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-666-77). Soft gelatin capsules, 20 mg (maroon), imprinted "SR". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-666-77).

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

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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 Sorret 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.

Weight or appetite, school or work performance, or other performance during Sorret treatment. 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 Sorret, 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 Sorret, 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 Sorret, I agree to stop using Sorret and tell my prescriber right away if any of the following happens to me:

- 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 Sorret, and to check for signs of side effects. Sorret, to check my progress, and to check for signs of side effects.

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

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 Sorret treat-

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

What are the possible side effects of Sorret?

Sorret has possible serious side effects

- Sorret can cause birth defects, premature births, and death in babies whose mothers took Sorret capsules while they were pregnant. See "What is the most important information I should know about Sorret?" and "What are the important warnings for females taking Sorret?"
- Serious mental health problems. See "What is the most important information I should know about Sorret?"
- Serious brain problems. Sorret can increase the pressure in your brain. This can lead to loss of sight, or in rare cases, death. Stop taking Sorret and call your prescriber right away if any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, or vomiting. Also, some patients taking isotretinoin capsules have had seizures (convulsions) or vomiting.
- Abdomen (stomach area) problems. Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better after you stop taking Sorret. Stop taking Sorret and call your prescriber if you get severe chest or bowel pain, trouble swallowing or painful swallowing, new or worsening heartburn, or rectal bleeding, yellowing of your skin or eyes, or dark urine.
- Bone and muscle problems. Sorret may affect bones, muscles, and ligaments and cause pain in joints or muscles. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are also some reports of broken bones or reduced healing of broken bones after taking isotretinoin capsules for acne as directed. No one knows if taking Sorret for acne will affect bones. If you have a broken bone, tell your provider that you are taking Sorret. Muscle weakness or without pain can be a sign of serious muscle damage. If this happens, stop taking Sorret and call your prescriber right away.
- Hearing problems. Some people taking isotretinoin capsules have developed hearing problems possible that hearing loss can be permanent. Stop using Sorret and call your prescriber if you get worse or if you have ringing in your ears.
- Vision problems. While taking Sorret you may develop a sudden inability to see in the driving at night can be dangerous. This condition usually clears up after you stop taking Sorret capsules, but it may be permanent. Other serious eye effects can occur. Stop taking Sorret if your prescriber right away if you have any problems with your vision or dryness of the eyes is painful or constant.
- Lipid (fats and cholesterol in blood) problems. Many people taking isotretinoin capsules have high levels of cholesterol and other fats in their blood. This can be a serious problem. Tell your prescriber for blood tests to check your lipids and to get any needed treatment. These generally go away when isotretinoin capsules treatment is finished.

month, including the following information:

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 Sorate in any amount even for short periods of time. This is why I must not be pregnant while taking Sorate.

Prescriber Signature: _____ Date: _____

Prescriber Signature: _____ Date: _____

MEDICATION GUIDE:

MEDICATION GUIDE:

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

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

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

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

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

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

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1. Birth defects. Sorate 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 Sorate if you are pregnant or plan to become pregnant while you are taking Sorate. Do not get pregnant for 1 month after you stop taking Sorate. Also, if you get pregnant while taking Sorate, stop taking it right away and call your prescriber.

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

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

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.

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

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

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What are the important warnings for females taking Sorate?

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

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

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

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

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

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

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

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

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

(Patient's Name)

understand that I must not take Sorate if I am pregnant.

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 Sorate.

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).

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.

understand that I will talk with my prescriber about any drugs or herbal products I plan to take during my Sorate 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).

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.

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

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

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

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

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

I have read and understand the materials my prescriber has given to me, including the Patient Product Information, Important Information Concerning Your Treatment with Sorate™ (Isotretinoin). 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).

understand that I must stop taking Sorate 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 birth control methods at any time.

understand that I must stop taking Sorate 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 birth control methods at any time.



CAUSES BIRTH DEFECTS

Special Instructions to Pharmacists:

- Do not fill Soretret prescriptions without a Qualification Sticker.
- Dispense a Medication Guide with each Soretret prescription, as required by law (available from Ranbaxy).
- Dispense only a 30-day supply.

**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



Isotretinoin Capsules, USP

SOTRETTM

NDC 68304-586-77

RANBAXY

Procedure for Pharmacist:

- Verify that the Soretret 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 Soretret prescription, as required by law (available from Ranbaxy by calling 1-866-431-8179).

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DO NOT GET PREGNANT

RANBAXY

NDC 68304-586-77

SOTRETTM

Isotretinoin Capsules, USP



100 Capsules
(10 x 10 Prescription Packs)

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

PROTECT FROM LIGHT

MEDICATION GUIDE FOR ALL PATIENTS
SOTRET™
ISOTRETINOIN CAPSULES, USP



50222870

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

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

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

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

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 Sotret, see "What are the possible side effects of Sotret?" in this Medication Guide.

What are the important warnings for females taking Sotret?

You must not become pregnant while taking Sotret, or for 1 month after you stop taking Sotret. Sotret can cause severe birth defects in babies of women who take it while they are pregnant, even if they take Sotret 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 Sotret. Taking Sotret also increases the chance of miscarriage and premature births. Female patients will not get their first prescription for Sotret unless there is proof they have had 2 negative pregnancy tests. The first test must be done when your prescriber decides to prescribe Sotret. The second pregnancy test must be done during the first 5 days of the menstrual period right before starting Sotret 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 Sotret unless there is proof that they have had a negative pregnancy test. A yellow self-adhesive Sotret Qualification Sticker on your prescription indicates to the pharmacist that you are qualified by your prescriber to get Sotret.

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

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

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

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

All patients should read the rest of this Medication Guide.

What are the signs of mental problems?

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

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

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

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What is Sotret?

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

Who should not take Sotret?

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

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.

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

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

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

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What is Sotret?

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

Who should not take Sotret?

- **Do not take Sotret if you are pregnant, plan to become pregnant, or become pregnant during Sotret treatment.** Sotret causes severe birth defects. All females should read the section "What are the important warnings for females taking Sotret?" for more information and warnings about Sotret and pregnancy.

Do not take Sotret unless you completely understand its possible risks and are willing to follow all of the instructions in this Medication Guide. Tell your prescriber if you or someone in your family has had any kind of mental problems, asthma, liver disease, diabetes, heart disease, osteoporosis (bone loss), weak bones, anorexia nervosa (an eating disorder where people eat too little), or any other important health problems. Tell your prescriber about any food or drug allergies you have had in the past. These problems do not necessarily mean you cannot take Sotret, but your prescriber needs this information to discuss if Sotret is right for you.

How should I take Sotret?

- You will get no more than a 30-day supply of Sotret at a time, to be sure you check in with your prescriber each month to discuss side effects.
- Your prescription should have a special yellow self-adhesive sticker attached to it. The sticker is YELLOW. If your prescription does not have this yellow self-adhesive sticker, call your prescriber. The pharmacy should not fill your prescription unless it has the yellow self-adhesive sticker.
- The amount of Sotret you take has been specially chosen for you and may change during treatment.
- You will take Sotret 2 times a day with a meal, unless your prescriber tells you otherwise. Swallow your Sotret with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.

If you miss a dose, just skip that dose. Do **not** take 2 doses the next time.

- You should return to your prescriber as directed to make sure you don't have signs of serious side effects. Because some of Sotret's serious side effects show up in blood tests, some of these visits may involve blood tests (monthly visits for female patients should always include a urine or serum pregnancy test).

What should I avoid while taking Sotret?

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

What are the possible side effects of Sotret?

Sotret has possible serious side effects

- **Sotret can cause birth defects, premature births, and death in babies** whose mothers took isotretinoin capsules while they were pregnant. See "What is the most important information I should know about Sotret?" and "What are the important warnings for females taking Sotret?"
- **Serious mental health problems.** See "What is the most important information I should know about Sotret?"
- **Serious brain problems.** Sotret can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Sotret and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking isotretinoin capsules have had seizures (convulsions) or stroke.
- **Abdomen (stomach area) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Sotret. Stop taking Sotret and call your prescriber if you get severe stomach, chest or bowel pain, trouble swallowing or painful swallowing, new or worsening heartburn, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine.
- **Bone and muscle problems.** Sotret may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your prescriber if you plan vigorous physical activity during treatment with Sotret. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are reports that some patients have had stunted growth after taking isotretinoin capsules for acne as directed. There are also some reports of broken bones or reduced healing of broken bones after taking isotretinoin capsules for acne as directed. No one knows if taking Sotret for acne will affect your bones. If you have a broken bone, tell your provider that you are taking Sotret. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens, stop taking Sotret and call your prescriber right away.
- **Hearing problems.** Some people taking isotretinoin capsules have developed hearing problems. It is possible that hearing loss can be permanent. Stop using Sotret and call your prescriber if your hearing gets worse or if you have ringing in your ears.
- **Vision problems.** While taking Sotret you may develop a sudden inability to see in the dark, so driving at night can be dangerous. This condition usually clears up after you stop taking isotretinoin capsules, but it may be permanent. Other serious eye effects can occur. Stop taking Sotret and call your prescriber right away if you have any problems with your vision or dryness of the eyes that is painful or constant.
- **Lipid (fats and cholesterol in blood) problems.** Many people taking isotretinoin capsules develop high levels of cholesterol and other fats in their blood. This can be a serious problem. Return to your prescriber for blood tests to check your lipids and to get any needed treatment. These problems generally go away when isotretinoin capsules treatment is finished.
- **Allergic reactions.** In some people, isotretinoin capsules can cause serious allergic reactions. Stop taking Sotret and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Sotret and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Sotret may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

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

Sotret has less serious possible side effects

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

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

This Medication Guide is only a summary of some important information about Sotret. Medicines are sometimes prescribed for purposes other than

pharmacist if you are not sure what type you are using.

- **Talk with your doctor if you plan to take other drugs or herbal products.** This is especially important for patients using birth control pills and other hormonal types of birth control because the birth control may not work as effectively if you are taking certain drugs or herbal products. You should not take the herbal supplement St. John's Wort because this herbal supplement may make birth control pills not work as effectively.
- **Talk with your doctor if you are currently taking an oral or injected corticosteroid or anticonvulsant (seizure) medication prior to using Sotret.** These drugs may weaken your bones.
- **Do not share Sotret with other people.** It can cause birth defects and other serious health problems.
- **Do not take Sotret with antibiotics unless you talk to your prescriber.** For some antibiotics, you may have to stop taking Sotret until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain.

What are the possible side effects of Sotret?

Sotret has possible serious side effects

- **Sotret can cause birth defects, premature births, and death in babies** whose mothers took isotretinoin capsules while they were pregnant. See "What is the most important information I should know about Sotret?" and "What are the important warnings for females taking Sotret?"
- **Serious mental health problems.** See "What is the most important information I should know about Sotret?"
- **Serious brain problems.** Sotret can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Sotret and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking isotretinoin capsules have had seizures (convulsions) or stroke.
- **Abdomen (stomach area) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Sotret. Stop taking Sotret and call your prescriber if you get severe stomach, chest or bowel pain, trouble swallowing or painful swallowing, new or worsening heartburn, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine.
- **Bone and muscle problems.** Sotret may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your prescriber if you plan vigorous physical activity during treatment with Sotret. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are reports that some patients have had stunted growth after taking isotretinoin capsules for acne as directed. There are also some reports of broken bones or reduced healing of broken bones after taking isotretinoin capsules for acne as directed. No one knows if taking Sotret for acne will affect your bones. If you have a broken bone, tell your provider that you are taking Sotret. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens, stop taking Sotret and call your prescriber right away.
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- **Signs of other possibly serious problems.** Sotret may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

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

Sotret has less serious possible side effects

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

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

This Medication Guide is only a summary of some important information about Sotret. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about Sotret, ask your prescriber. Do not use Sotret for a condition for which it was not prescribed.

Active Ingredient: Isotretinoin.

Inactive Ingredients: 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 systems: 10 mg - iron oxide (red) and titanium dioxide; 20 mg - FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg - FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

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

November 2002

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

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

Procedure for Pharmacist:

- Verify that the Sotret 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 Sotret prescription, as required by law (available from Ranbaxy by calling 1-866-431-8179).

APPROVED

Non Varnish Area

RANBAXY

NDC 63304-584-77

SOTRETTM
100 Capsules, USP

10 mg

Each capsule contains
10 mg Isotretinoin, USP

Capsules
(Prescription Packs)

Procedure for Pharmacist:

- Verify that the Soret 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 Soret prescription, as required by law (available from Ranbaxy by calling 1-866-431-8179).

Rx only

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Special Instructions to Pharmacists:

- Do not fill Soret prescriptions without a Qualification Sticker.
- Dispense a Medication Guide with each Soret prescription, as required by law (available from Ranbaxy).
- Dispense only a 30-day supply.



RANBAXY

NDC 63304-584-77

SOTRETTM
100 Capsules, USP

10 mg

100 capsules
(10 x 10 Prescription Packs)

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

PROTECT FROM LIGHT

ISOTRETINION
Capsule USP
20 mg

Manufactured for:
Parke-Davis Pharmaceutical Company
Kenilworth, NJ 07033 USA
Patented in the United States
by Parke-Davis, 110 019, 1102
by New Delhi, 110 019, 1102

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

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by New Delhi, 110 019, 1102

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

5022213

Isotretinion 20 mg Blister Foil
Blister Size - 99 x 70 mm
Foil Width - 208 mm
RLL/PKGDEV - 26/09/02

ISOTRETINION
 40 mg Capsule USP
 NDC 5040-988-11
 Manufactured for: Paragon Pharmaceuticals, Inc. Parsippany, NJ 08859-0100, USA. Distributed by: Paragon Pharmaceuticals, Inc. Parsippany, NJ 08859-0100, USA. New Delhi - 110 019, India.

CAUSES BIRTH DEFECTS
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 DO NOT GET PREGNANT

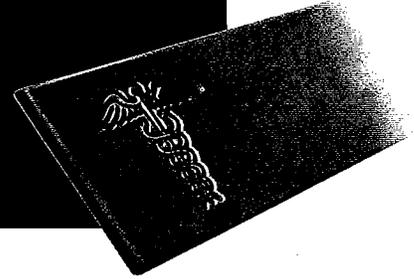
5022214

Isotretinoin 40 mg Blister Foil
 Blister Size - 99 x 70 mm
 Foil Width - 408 mm
 RLL/PKGDEV - 26/09/02



Ranbaxy Pharmaceuticals, Inc.
600 College Road East
Princeton, NJ 08540
www.ranbaxyusa.com

SOTRET™ (ISOTRETINOIN CAPSULES)



PRESCRIBING PROCEDURES FOR SOTRET

Dear Sotret Prescriber:

Ranbaxy Pharmaceuticals Inc., in cooperation with the FDA, is announcing the *Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity™ (I.M.P.A.R.T.™)*. I.M.P.A.R.T. has been developed because data has shown that despite extensive warnings, pregnant women continue to receive isotretinoin and women continue to become pregnant while taking isotretinoin.

Therefore it is imperative that female patients are **qualified** under I.M.P.A.R.T. to receive a Sotret prescription. Specifically, they must have:

- Negative pregnancy tests throughout the treatment course (2 at initiation of therapy and then one test monthly)
- Selected and committed to use 2 forms of effective contraception; counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis
- Signed informed consent
- Been informed of the purpose and importance of participating in the Isotretinoin Survey and given the opportunity to enroll

Please see package insert for full information: The boxed **CONTRAINDICATIONS AND WARNINGS (Black Box)** in the package insert contains complete Female Patient Qualification Criteria. These are reproduced below under "Details of I.M.P.A.R.T. Components." Please note that both Informed Consent/Patient Agreement and Patient Information/Consent forms and the patient Medication Guide are now included in the package insert. These have been revised for implementation of I.M.P.A.R.T.

Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity (I.M.P.A.R.T.)

I.M.P.A.R.T. will be described fully within the boxed **CONTRAINDICATIONS AND WARNINGS (Black Box)** and the **PRECAUTIONS** sections of the Sotret package insert. The following list is the necessary steps prescribers must take to be in compliance with the risk management components of the newly revised Sotret package insert.

To receive the first shipment of Sotret Qualification Stickers:

1. **Read the I.M.P.A.R.T.™ Guide to Best Practices**
2. **Sign and return, in the postage paid envelope provided, the completed I.M.P.A.R.T. Letter of Understanding, which states:**

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- I know the risk and severity of fetal injury/birth defects from Sotret
- 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 Sotret therapy and for a month after stopping Sotret. To help patients have the knowledge and tools to do so: before beginning treatment of female patients with Sotret, I will refer for expert, detailed pregnancy prevention counseling and prescribing, reimbursement 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 Sotret treatment course, the I.M.P.A.R.T. procedures for Sotret, including monthly pregnancy avoidance counseling, pregnancy testing and use of Sotret Qualification Stickers

Additional Stickers can then be obtained as needed by calling 1-866-431-8179 (details below).

Prior to writing the Sotret prescription:

Obtain screening and confirmation pregnancy tests for ALL female patients. Ensure each female patient is *qualified* according to criteria identified in the CONTRAINDICATIONS AND WARNINGS (Black Box) section of the package insert.

Monthly visits:

1. Obtain a monthly pregnancy test for ALL female patients. Repeat counseling about contraception and behaviors associated with an increased risk of pregnancy and encourage women who have not yet enrolled in the Isotretinoin Survey to do so.
2. Affix a yellow *Sotret Qualification Sticker* on each Sotret prescription for both male and female patients (details below); phoned, faxed, or electronic prescriptions are not acceptable.
3. Prescribe no more than a 30-day supply of Sotret.

Details of I.M.P.A.R.T. components:

Criteria for Female Patient Qualification:

Female patients of childbearing potential must meet specific criteria to be qualified to receive a Sotret prescription every month they are on Sotret treatment. These criteria are found in the CONTRAINDICATIONS AND WARNINGS (Black Box) section of the package insert. For female patients, the yellow self-adhesive Sotret Qualification Sticker signifies that she:

- **Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Sotret prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Sotret. The second pregnancy test (a confirmation test) should be done during the first five days of the menstrual period immediately preceding the beginning of Sotret 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 two 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.**

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- **Must have selected and has committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of effective contraception for at least one month prior to initiation of Sotret therapy, during Sotret therapy, and for one month after discontinuing Sotret 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 child-bearing potential use two effective forms of contraception simultaneously. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Sotret. 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 Sotret. 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.

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

Ranbaxy supports an initial referral to a health care provider trained to provide family planning services for contraceptive counseling should you feel that this is necessary. A referral form is contained within the female Sotret Program to Prevent Pregnancy (PPP)TM documentation. *The PPP is a systematic approach to comprehensive patient education that assists patients in understanding their responsibilities* and includes education for contraception compliance and reinforcement of educational messages.

Sotret Qualification Stickers

Prescribers must obtain yellow self-adhesive Sotret Qualification Stickers designed to adhere to the center portion of the patient's Sotret prescription (see enclosed example). The Sotret Qualification Stickers can only be obtained by reading the *I.M.P.A.R.T. Guide to Best Practices* and signing and returning the completed *I.M.P.A.R.T. Letter of Understanding*.

The Guide and the letter are enclosed. Additional Sotret Qualification Stickers can be obtained by calling toll-free at 1-866-431-8179. This number is also found in the Guide.

These Sotret Qualification Stickers will serve as documentation to pharmacists that the patient has been qualified by the prescriber as an appropriate patient for Sotret therapy. Pharmacists will have the option to verify the authorization for the Sticker by calling 1-866-431-8179, but this step is not required. Sotret prescriptions for female patients of childbearing potential should not be filled more than seven days after patient qualification.

The Sotret Qualification Sticker should also be used on prescriptions for **male patients**. Thus, *ALL prescriptions for Sotret should have a yellow self-adhesive Sotret Qualification Stickers.*

I.M.P.A.R.T. outcomes

To measure the effectiveness of I.M.P.A.R.T., Ranbaxy will use several outcome approaches.

- Ranbaxy will continue to review the number of women who join the Isotretinoin Survey conducted by the Slone Epidemiology Center of the Boston University School of Public Health. Ranbaxy has committed to increasing enrollment of female patients to 60% from 25-40% currently. Your help is vital to achieving this critically important objective. The Survey is necessary for accurate identification of program problems and timely implementation of solutions. We therefore ask prescribers to strongly encourage all female patients between 12 and 59 years of age, irrespective of pregnancy risk, to join the Isotretinoin Survey. An application form is contained inside both the female PPP kits and in the Sotret blister packs.
- A new audit of pharmacies will be performed to assess the use of the yellow self-adhesive Sotret Qualification Stickers. As part of the validation for this component, the audit will be a check on the use of the yellow self-adhesive Sotret Qualification Stickers. The data collected will not identify patients or prescribers.

Continuing Medical Education Credit is Available

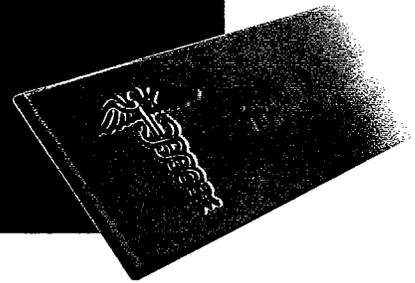
Ranbaxy has supported a CME program on teratogenic drugs, pregnancy testing, effective contraception, limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure, and methods to evaluate pregnancy risk. To find out how to register for the half-day course, or receive a self-study program, please call 1-866-431-8179.

Thank you for participating in this important risk management initiative. If you have any questions concerning this program or would like to obtain a copy of the (I.M.P.A.R.T.™) Guide to Best Practices and the I.M.P.A.R.T. Letter of Understanding, please call Ranbaxy at 1-866-431-8179.

Sincerely yours,

Ranbaxy Pharmaceuticals, Inc.
enclosures

5021246 November 2002

SOTRET™
(ISOTRETINOIN CAPSULES)****DISPENSING PROCEDURES FOR SOTRET****

Dear Pharmacist:

This letter contains dispensing procedures for Sotret.

Sotret causes severe birth defects. Ranbaxy Pharmaceuticals, Inc., provides the Program to Prevent Pregnancy (PPP) along with the risk management program called *Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity™ (I.M.P.A.R.T.™)*.

Please process ALL prescriptions for Sotret as follows:

1. Dispense Sotret only upon presentation of a prescription with a yellow self-adhesive Sotret Qualification Sticker that has been completely and correctly filled in by the prescriber (see example in enclosure). Telephone, fax, and computer-generated orders for Sotret are no longer acceptable.
2. Dispense a maximum of a 30-day supply of Sotret. Quantities in excess of a 30-day supply are not acceptable.
3. Refills are not acceptable. Dispense more Sotret only upon presentation of a new prescription with a yellow self-adhesive Sotret Qualification Sticker.
4. Fill Sotret prescriptions for female patients within 7 days from the date of qualification noted on the yellow self-adhesive Sotret Qualification Sticker. Prescriptions presented more than 7 days from the qualification date are considered expired, and should not be honored.
5. The Medication Guide must be dispensed to every patient with every Sotret prescription, as required by law.
6. If you wish to verify a prescriber's authorization to prescribe Sotret, call 1-866-431-8179. Use the unique identifier number located on each yellow self-adhesive Sotret Qualification Sticker. This verification is not a requirement for dispensing Sotret.

The Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity (I.M.P.A.R.T.) will be described fully within the boxed CONTRAINDICATIONS AND WARNINGS (Black Box) and PRECAUTIONS sections of the Sotret package insert.

Sotret should be dispensed only for prescriptions which bear the yellow self-adhesive Sotret Qualification Sticker. If you receive a Sotret prescription without a yellow self-adhesive Sotret Qualification Sticker, you should call the prescriber.

What does the Qualification Sticker Signify?

Under the I.M.P.A.R.T. Program, "qualification" by the prescriber means that the female patient:

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25mIU/mL, before the initial Sotret prescription is written. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Sotret. The second pregnancy test (a confirmation test) should be done during the first five days of the menstrual period immediately preceding the beginning of Sotret therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated every month prior to the female patient receiving each prescription.
- Must have selected and committed to use two forms of effective contraception simultaneously, at least one 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 Sotret therapy, during Sotret therapy, and for 1 month after discontinuing Sotret therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.
- Must have signed a Patient Information/Consent form that contains warnings about the risk of birth defects if the fetus is exposed to Sotret.
- Must have been informed of the purpose and importance of participating in the Isotretinoin Survey, and have been given the opportunity to enroll.

How is the Qualification Sticker Used?

The yellow self-adhesive Sotret Qualification Sticker is sized to fit in the middle of the physician's prescription blank, and once affixed it cannot be removed without destroying the blank (See enclosed example).

Each time Sotret is prescribed, the prescriber will indicate the date of female patient qualification on the yellow self-adhesive Sotret Qualification Sticker, and affix the sticker to the prescription blank. The sticker will include the following information:

- A space for the prescriber to indicate the date on which the female patient was qualified to receive a Sotret prescription.
- A check box to indicate the gender of the patient (ALL prescriptions should have the yellow self-adhesive sticker).
- A notice that the prescription must be filled within 7 days of the qualification date.
- An instruction to dispense no more than a 30-day supply only, with no refills on the prescription, no phone or electronic orders.

Thank you for participating in this important risk management initiative. You can further contribute to the success of this program by encouraging all female patients between 12 and 59 years of age

irrespective of pregnancy risk to enroll in the Isotretinoin Survey conducted by the Slone Epidemiology Center of Boston University School of Public Health. This confidential Survey will collect and analyze data to help Ranbaxy and FDA decide if I.M.P.A.R.T. is helping to prevent exposure of pregnant women to Sotret. A new, voluntary audit of pharmacies by Ranbaxy is also planned to assess use of the yellow self-adhesive Sotret Qualification Stickers. If you are contacted, please participate in this important public health endeavor.

Sincerely yours,

Ranbaxy Pharmaceuticals, Inc.
enclosures

5021246 November 2002

DEC 2 9 17

APPROVED

Ranbaxy Sotret Qualification Sticker

SOTRET™ QUALIFICATION STICKER Female Male

Female patient has been qualified as described in the
CONTRAINDICATION AND WARNINGS of package insert on _____
Qualification date

Pharmacist

- Fill within 7 days of qualification date
- No more than 30-day supply ONLY
- NO refills allowed
- For Human use ONLY

XXXXXX

DEA# AB XXXXX

Ranbaxy Pharmaceuticals Inc.

APPROVED

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-041

CSO LABELING REVIEW(S)

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

ANDA Number: 76-041

Date of Submission: November 11, 2002
December 2, 2002

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 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 November 11, 2002 submission (Vol 9.1,9.3, 9.5)*
2. CARTON - 100s (10 x 10) – *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.1,9.3, 9.5)*
3. INSERT – *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.1, 9.3, 9.5)*
4. ISOTRETINOIN MEDICATION PROGRAM ALERTING THE RISKS OF TERATOGENICITY IMPART™ Guide to Best Practices - *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2, 9.4, 9.6)*
 - LETTER OF UNDERSTANDING TO PRESCRIBERS – *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2, 9.4, 9.6)*
5. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN SOTRET PROGRAM TO PREVENT PREGNANCY AND RISK MANAGEMENT PROGRAM FOR WOMEN - *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2,9.4, 9.6)*
 - ISOTRETINOIN SURVEY FORM - *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2,9.4, 9.6)*
 - INFORMED CONSENT/PATIENT AGREEMENT (All Patients) - *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2,9.4, 9.6)*
 - INFORMED CONSENT/PATIENT AGREEMENT (for female patients) - *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2,9.4, 9.6)*
 - QUALIFICATION CHECKLIST- *Satisfactory in FPL as of the November 11, 2002 submission (Vol 9.2,9.4, 9.6)*
6. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN SOTRET™ (isotretinoin) RISK MANAGEMENT FOR MEN – *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.2, 9.4,9.6)*
7. RECOGNIZING PSYCHIATRIC DISORDERS IN ADOLESCENTS AND YOUNG ADULTS: A Guide For Prescribers Of Sotret (Isotretinoin) - *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.2,9.4,9.6)*
8. SOTRET QUALIFICATION STICKER – *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.1, 9.3,9.5)*
9. PRESCRIBING PROCEDURES FOR SOTRET™ (ISOTRETINOIN) - *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.1, 9.3, 9.5)*
10. DISPENSING PROCEDURES FOR SOTRET™ (ISOTRETINOIN) CAPSULES - *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.1, 9.3, 9.5)*

11. MEDICATION GUIDE - *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.1, 9.3, 9.5)*
12. ISOTRETINOIN PRESCRIPTION COMPLIANCE SURVEY - Under review but not a part of labeling. However, must be acceptable to ODS before this application can be approved.
13. ISOTRETINOIN SURVEY FORM (for females only) – *Satisfactory in FPL as of the November 11, 2002 submission. (Vol 9.1, 9.3, 9.5)*
14. DISPENSING GUIDE - *Satisfactory in FPL as of the December 2, 2002 submission. (Vol 9.1)*

Revisions needed post-approval:

Firm has provided a commitment to make the following revisions pre commercial marketing.

1. GENERAL - Please refer to the "yellow self adhesive Sotret sticker" as "yellow self adhesive isotretinoin sticker" throughout your labeling.
2. UNIT DOSE BLISTER PACK -Special Warnings for Female Patients; bold the two sentences, "Sotret causes birth defects. Do NOT take Sotret if you are pregnant."
3. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN SOTRET PROGRAM TO PREVENT PREGNANCY AND RISK MANAGEMENT PROGRAM FOR WOMEN
 - a. Table of contents –Section 3-Replace " _____ ," with "Isotretinoin Survey"
 - b. INFORMED CONSENT/PATIENT AGREEMENT- change to "PATIENT INFORMATION/CONSENT (for female patients....)"
4. SOTRET™ QUALIFICATION STICKER - Include the established name on your qualification sticker.
5. PRESCRIBING PROCEDURES FOR SOTRET™ - Page 47, IMPART Outcomes- Delete the sentence beginning with "Ranbaxy has committed to increasing.....currently." Since this is a new program for you.
6. DISPENSING PROCEDURES FOR SOTRET™-Page 48, Please process ALL prescriptions for Sotret as follows-number 1, last sentence-revise to read "...computer generated orders for Sotret are not acceptable".

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)			
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? Yes, per Nashed Nashed
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? Yes per Nashed Nashed

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. This is considered a tentative decision and this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. The applicant has been informed.

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.1.11; Section XIII; p.2862) 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, Nashed Nashed 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.

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 10 mg capsules are light pink, imprinted "5R"; the 20 mg capsules are maroon, imprinted "6R"; the 40 mg capsules are yellow, imprinted "7R".

6. Manufacturer

Ranbaxy Laboratories Limited

India

(Vol A. 1.10: Section IX; p.241)

7. Inactive Ingredients

There does not appear to be a discrepancy in inactives between the labeling and the C&C Statements. (Vol. A. 1.10; Section VII; p.2202)

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.

9. Bioequivalence issues –Satisfactory 4/30/02

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:
December 16, 2002

Dates of Submission:
November 11, 2002 (Amendment)
December 2, 2002 (Amendment)

Primary Reviewer:
Michelle Dillahunt

Date: 10/18/02

Acting Team Leader:
Lillie Golson

Date: 12/18/02

cc: ANDA: 76-041
DUP/DIVISION FILE
HFD-613/M Dillahunt/LGolson (no cc)
\\CDS013\OGDS11\FIRMSNZ\ANBAXY\LTRS&REV\76041ap.l.doc
Review

- d. In the "Warnings To Female Patients" between the blister, replace " _____" with "DO NOT GET PREGNANT".
 - e. Please ensure that a medication guide and a survey enrollment form are included in each blister.
3. CARTON - 100s (10 x 10) - See GENERAL COMMENT (1e)

4. INSERT

a. GENERAL COMMENTS

See GENERAL COMMENTS (1 a, b and e)

- b. WARNINGS - Create a new subsection beginning with the second sentence of the seventh paragraph, "Animal Studies".
- c. PATIENT INFORMATION/CONSENT FORM (For female patients concerning birth defects) - Satisfactory in draft.
- d. INFORMED CONSENT/PATIENT AGREEMENT FORM (All Patients) – Satisfactory in draft.
- e. MEDICATION GUIDE – Satisfactory in draft.

5. ISOTRETINOIN MEDICATION PROGRAM ALERTING THE RISKS OF TERATOGENICITY
IMPART™ Guide to Best Practices

a. See GENERAL COMMENTS

- b. As discussed with you previously and upon further evaluation, your program name is still not grammatically correct. To not compromise the IMPART name, we suggest *"Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity"* for your consideration.

c. _____

- i. We have serious misgivings about the suitability of the word " _____"

Since you cannot use the same name for your plan as Roche, perhaps you can retain the word "pregnancy" and substitute the other words (for example, Plan to Prevent Pregnancy or Program to Prevent Pregnancy).

- ii. We also question the validity of the word " _____" in this context.

d. On page 2:

- i. Under "Important Facts About Isotretinoin", change the second bullet to read; Treatment with isotretinoin during pregnancy is contraindicated. Female patients should not be pregnant.....
 - ii. Under "The IMPART Guide to Best Practices"-revise the second sentence to read: Please refer to the isotretinoin capsules CONTRAINDICATIONS AND WARNINGS and the Precautions of the isotretinoin capsules Product Information.
 - iii. Under "To obtain these stickers", italicize "Isotretinoin" since it is part of the title of the booklet.
 - iv. Please revise your CONTRAINDICATIONS AND WARNINGS to be in accord with the revised approved Accutane labeling (S-051).
- e. On page 3, under the heading "About Isotretinoin", second paragraph – bold "Isotretinoin is teratogenic".

- p. On the back of the booklet, under "Where to find information", correct the spelling of "enrollment" in the last section, "Isotretinoin Survey Enrollment Form".

6. LETTER OF UNDERSTANDING TO PRESCRIBERS

- a. GENERAL COMMENT- Please revise the Letter of Understanding to Prescribers for relevance to the current situation. Specifically, explain to prescribers that your risk management program booklets and forms contain the same information as the Roche S.M.A.R.T. program. Also clearly delineate any components added or deleted. For example, prescribers should know that you are not providing phone information in languages other than English and Spanish.
- b. Underline "Must" in the 6th and 7th bullets.

7. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN ISOTRETINOIN PREGNANCY PREVENTION AND RISK MANAGEMENT PROGRAM FOR WOMEN

- a. See GENERAL COMMENTS
- b. We find the use of white print against a beige background very difficult to read. We suggest selecting colors with better contrast.
- c. On page 1.2, "Things you should know about"- bold the second paragraph, "Possible serious side..."
- d. On page 1.3, Facts about nodular acne. Please arrange your pictures in the same sequence of acne pathogenesis as the RLD.
- e. On page 1.4, "How should you take isotretinoin" – replace _____ with "30 day".
- f. On page 1.5, under the heading "Important Information for All Patients": fifth bullet- change "mother" to "mothers" and include the page number where the section can be referenced.
- g. Isotretinoin Capsules, Informed Consent/Patient Agreement (for all patients) - move the sentence beginning with "Do not sign ..." to the next line.
- h. Isotretinoin Capsules, Patient Information/Consent (for all female patients) - move the sentence beginning with "Do not sign ..." to the next line and replace "agreement" with "consent". Place a period after understand and delete the last part of the sentence (about all)
- i. On page 3.14, "Condom", 3rd paragraph - add the sentence below as the fifth sentence:
However, since it is necessary to use a spermicide with a condom, this can be used as a lubricant.
- j. On page 3.23, "Isotretinoin InfoLine"; English –use lower case for the word "We'd".
- k. On page 3.24, "Scenes from the Video".
- i. We find the title of your video _____ unacceptable because there is no such thing. The only certain way to prevent pregnancy is absolute abstinence. Please revise the title.
- ii. We consider your photos to be highly "promotional" (close-up face photos of happy, sensual-looking young women with perfect skin). Such photographs are distracting and peripheral to the meaning of these booklets, which is safety, not efficacy. Furthermore, the pictures suggest that all patients who take isotretinoin achieve perfect skin. Aside from the perhaps 1 in 3 patients for whom the drug is not curative, many patients with nodular acne are left with scarring.
- iii. We also question the advice "check your diaphragm regularly". This suggests diaphragms, like IUDs (not "checkable" by patient) remain in place all of the time.

8. BE CLEVER/ BE CAUTIOUS/ BE CERTAIN
ISOTRETINOIN CAPSULES RISK MANAGEMENT FOR MEN

- a. See GENERAL COMMENTS
- b. The color of the cover of your booklet is too dark for prescribers to legibly fill in the contact phone numbers unless they have a special white ink pen on hand. Please consider selecting a lighter color.
- c. Reproduction information for men:
Fourth paragraph - create a new paragraph for " In addition, male patients should read... "
- d. On page 1.4 under the heading, How should I Take Isotretinoin?- replace ' _____ ' with "30-day".
- e. On page 1.5, under the heading, "Important Information for All Patients"
 - i. Fifth bullet- change " _____ " to "mothers".
 - ii. Fifth and sixth bullet- include the page numbers where the sections can be referenced.
- f. On page 1.6, under the heading, "Isotretinoin has more common, less serious....," fourth paragraph- create a new paragraph for the sentence beginning with "Medicines".
- g. Isotretinoin Capsules, Informed Consent/Patient Agreement (for all patients) - move the sentence beginning with "Do not sign" to the next line.
- h. Isotretinoin InfoLine; English –use lower case for the word "We'd".

9. RECOGNIZING PSYCHIATRIC DISORDERS IN ADOLESCENTS AND YOUNG ADULTS: A Guide
For Prescribers Of Isotretinoin Capsules

See GENERAL COMMENTS.

10. ISOTRETINOIN QUALIFICATION STICKER – Satisfactory in draft.

11. PRESCRIBING PROCEDURES FOR ISOTRETINOIN CAPSULES

- a. Roche distributed this information as a STAT/GRAM to prescribers. How will you distribute this information to prescribers?
- b. Please use the text submitted in your 5/3/02 submission for your heading since your product has not been previously approved or prescribed.

12. DISPENSING PROCEDURES FOR ISOTRETINOIN CAPSULES:

- a. Roche distributed this information as a STAT/GRAM to pharmacists. How will you distribute this information to pharmacists?
- b. Please use the text submitted in your 5/3/02 submission for your heading and the first paragraph since your product has not been previously approved or prescribed.
- c. No. 2; change ' _____ ' to "30-day".
- d. No. 6; underline "not" in the last sentence.
- e. What does the Qualification Sticker Signify?
 - i. First bullet, second sentence – revise to read, The first test (a screening test) is
 - ii. First bullet, third sentence – revise to read, The second pregnancy test (a confirmation test) should ...

iii. First bullet, last sentence – revise to read, A pregnancy test must be repeated every month prior ...

iv. Second bullet, second sentence-revise to read;
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.

f. How is the Qualification Sticker Used?

Fourth bullet- change " _____ " to "30-day".

13. MEDICATION GUIDE - Satisfactory in draft.

14. ISOTRETINOIN PRESCRIPTION COMPLIANCE SURVEY

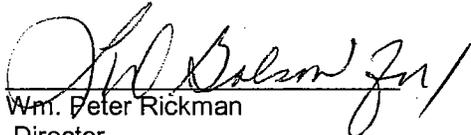
The following comment from the Office of Drug Safety was emailed to you on September 27, 2002.

Ranbaxy / IMS must add a validation component to their protocol for approval. This is an essential element for an isotretinoin prescription compliance survey. Additionally, Ranbaxy / IMS should select the largest of its proposed survey sample sizes (1,000 pharmacies) and collect data on all prescriptions encountered in the survey, not simply those for the Ranbaxy product. IMS / Ranbaxy should report to FDA the presence of any refill prescriptions encountered in the survey.

Please revise your labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Unit Dose Blister Label:

Unit Dose Carton Wallet Label: (10s)(2x5)

Unit Dose Carton Label: (10 x 10)

Professional Package Insert Labeling:

Informed Consent Form

Medication Guide:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

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 Wallet Labeling:

Basis of Approval for the Unit Dose Carton Labeling:

Other Comments:

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)			
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? *YLD MW 3/10/02*
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? *YLD MW 12/10/02*

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 not objections to the use of the proprietary name Sotret. This is considered a tentative decision and this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. The applicant has been informed.
3. Comments from the consult from the Division of Dermatologic and Dental Drug Products has been incorporated in this review.
4. 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.1.11; Section XIII; p.2862) 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 been asked to ensure that such is the case and the chemist has been asked whether or not such is the case.

5. Labeling

The firm has differentiated its product strengths by using different color contrast on their carton labeling.

Because this is a teratogenic drug product, special differentiation to avoid pregnancy is found throughout the labeling.

6. 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 10 mg capsules are light pink, imprinted "5R"; the 20 mg capsules are maroon, imprinted "6R"; the 40 mg capsules are yellow, imprinted "7R".

7. Manufacturer

Ranbaxy Laboratories Limited
India

(Vol A. 1.10: Section IX; p.241)

8. Inactive Ingredients

There does not appear to be a discrepancy in inactives between the labeling and the C&C Statements. (Vol. A. 1.10; Section VII; p.2202)

9. 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 – Same as RLD

10. Bioequivalence issues –Satisfactory 4/30/02

11. 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:
October 17, 2002

Dates of Submission:
November 30, 2000 (Original submission)
December 11, 2001 (Amendment)
December 20, 2001 (Amendment)
May 3, 2002 (Amendment)
August 5, 2002 (Amendment)
August 9, 2002 (Amendment)

Primary Reviewer:
Michelle Dillahunt

Date: 10/23/02



Acting Team Leader:
Lillie Golson

Date: 10/23/02



cc: ANDA: 76-041
DUP/DIVISION FILE
HFD-613/M Dillahunt/LGolson (no cc)
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Review

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-041

CHEMISTRY REVIEW(S)

Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 76-041 [Isotretinoin Capsules USP, 10 mg, 20 mg, and 40 mg]
3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East, Princeton, NJ 08540
Telephone: (609) 720-5612 (direct line); FAX: (609) 720-1155

Note:

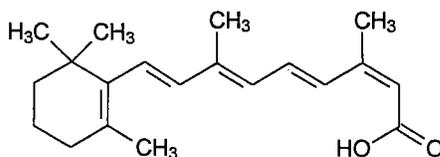
The Headquarters of Ranbaxy Laboratories Limited is located at Section -18, UDYOG VIHAR INDUSTRIAL AREA, Gurgaon-122001, India

4. LEGAL BASIS FOR SUBMISSION
The innovator's U.S. Patent No. 4,464,394 will expire on August 7, 2001. No marketing exclusivities have been granted to this drug product.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME _____
7. NONPROPRIETARY NAME Isotretinoin Capsules USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Ranbaxy:
11/30/00 Submission of ANDA (received at OGD 12/04/00)
01/10/01 Submission of FDA Form 3454

FDA:
01/09/01 Request for FDA Form 3454
01/11/01 Acknowledgment letter (acceptable for filing: 12/04/00)
10. PHARMACOLOGICAL CATEGORY
11. Rx or OTC Rx
12. RELATED IND/NDA/ANDA/DMFs
Innovator Product: Accutane® Capsules (Roche) [NDA #18-662]
10 mg and 40 mg strength: approved on 05/07/1982
20 mg strength: approved on 03/28/1983
See Item 37 for a list of DMFs referenced in the ANDA.
13. DOSAGE FORM Capsules
14. STRENGTH 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Isotretinoin. Retinoic acid, 13-*cis*-.C₂₀H₂₈O₂. 300.44. 4759-48-2.
Keratolytic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

Both Drug substance and drug product are listed in the USP 24. Type II DMF for the drug substance is inadequate. There are many other CMC deficiencies. Labeling review and bioequivalence review are pending. Method validation by FDA lab is not required. Acceptable EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Apprvable (MINOR AMENDMENT)

19. REVIEWER: Shing H. Liu, Ph.D.

DATE COMPLETED: 04/10/01 and on 04/20/01
(revised on May 10, 2001)

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Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 2
2. ANDA # 76-041 [Isotretinoin Capsules USP, 10 mg, 20 mg, and 40 mg]
3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East, Princeton, NJ 08540
Telephone: (609) 720-5612 (direct line); FAX: (609) 720-1155

Note:

The Headquarters of Ranbaxy Laboratories Limited is located at Section -18, UDYOG VIHAR INDUSTRIAL AREA, Gurgaon-122001, India

4. LEGAL BASIS FOR SUBMISSION
The innovator's U.S. Patent No. 4,464,394 expired on August 7, 2001. No marketing exclusivities have been granted to this drug product.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME _____
7. NONPROPRIETARY NAME Isotretinoin Capsules USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
* Denotes amendment reviewed in this chemistry review
Ranbaxy:
11/30/00 Submission of ANDA (received at OGD 12/04/00)
01/10/01 Submission of FDA Form 3454
07/17/01 *Submission of MINOR amendment
08/15/01 *Submission of additional trade name
09/21/01 *Submission of Bio amendment

FDA:
01/09/01 Request for FDA Form 3454
01/11/01 Acknowledgment letter (acceptable for filing: 12/04/00)
05/18/01 NA letter (MINOR) (based on CR #1 by S. Liu, Ph.D.)
06/20/01 Deficiency letter to Ranbaxy
10. PHARMACOLOGICAL CATEGORY
11. Rx or OTC Rx

12. RELATED IND/NDA/ANDA/DMFs

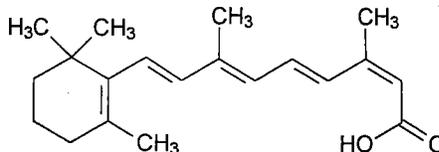
Innovator Product: Accutane® Capsules (Roche) [NDA #18-662]
10 mg and 40 mg strength: approved on 05/07/1982
20 mg strength: approved on 03/28/1983
See Item 37 for a list of DMFs referenced in the ANDA.

13. DOSAGE FORM Capsules

14. STRENGTH 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Isotretinoin. Retinoic acid, 13-*cis*-.C₂₀H₂₈O₂. 300.44. 4759-48-2.
Keratolytic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

Both Drug substance and drug product are listed in the USP 24. Type II DMF for the drug substance remains inadequate. There is another CMC deficiency regarding finished product impurity specifications. Labeling review is pending. Ranbaxy's response to the bioequivalence deficiency is under review. Method validation by FDA lab is not required. Acceptable EER is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable (MINOR AMENDMENT)

19. REVIEWER: Shing H. Liu, Ph.D.

DATE COMPLETED: 08/30/01 Revised on 09/13/01
Second revision: 09/24/01
Third revision: 10/01/01

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14

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Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 3
2. ANDA # 76-041 [Isotretinoin Capsules USP, 10 mg, 20 mg, and 40 mg]
3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East, Princeton, NJ 08540
Telephone: (609) 720-5612 (direct line); FAX: (609) 720-1155

Note:

The Headquarters of Ranbaxy Laboratories Limited is located at Section -18, UDYOG VIHAR INDUSTRIAL AREA, Gurgaon-122001, India

4. LEGAL BASIS FOR SUBMISSION
The innovator's U.S. Patent No. 4,464,394 expired on August 7, 2001. No marketing exclusivities have been granted to this drug product.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME
7. NONPROPRIETARY NAME Isotretinoin Capsules USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
* Denotes amendment under review in this chemistry review #3
Ranbaxy:
11/30/00 Submission of ANDA (received at OGD 12/04/00)
01/10/01 Submission of FDA Form 3454
07/17/01 Submission of MINOR amendment
08/15/01 Submission of additional trade name
09/21/01 Submission of Bio amendment
10/15/01 *Submission of MINOR amendment
12/04/01 Submission of Bio amendment
12/05/01 Submission of Bio amendment

FDA:

- 01/09/01 Request for FDA Form 3454
01/11/01 Acknowledgment letter (acceptable for filing: 12/04/00)
05/18/01 NA letter (MINOR) (based on CR #1 by S. Liu, Ph.D.)
06/20/01 Deficiency letter to Ranbaxy
10/03/01 NA letter (MINOR) (based on CR #2 by S. Liu, Ph.D.)

10. PHARMACOLOGICAL CATEGORY Anti-acne agent

11. Rx or OTC Rx

12. RELATED IND/NDA/ANDA/DMFs

Innovator Product: Accutane® Capsules (Roche) [NDA #18-662]

10 mg and 40 mg strength: approved on 05/07/1982

20 mg strength: approved on 03/28/1983

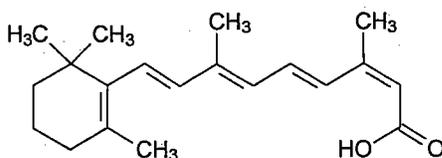
See Item 37 for a list of DMFs referenced in the ANDA.

13. DOSAGE FORM Capsules

14. STRENGTH 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Isotretinoin. Retinoic acid, 13-*cis*-.C₂₀H₂₈O₂. 300.44. 4759-48-2.
Keratolytic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

Both Drug substance and drug product are listed in the USP 24. Type II DMF for the drug substance was reviewed in connection with the MINOR amendment, and was found adequate. The applicant's response to the CMC deficiency regarding finished product impurity specifications is acceptable. Division of Bioequivalence issued a deficiency letter on 11/06/01, to which no response has been received. One of the bio deficiencies is related to the dissolution testing method. As such, additional more stability data are required as the result of a revised dissolution testing method.

Labeling review is pending. Method validation by FDA lab is not required. Acceptable EER is pending as the pre-approval inspection of the applicant in India is scheduled in late November 2001.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable (MINOR AMENDMENT)

19. REVIEWER: Shing H. Liu, Ph.D. DATE COMPLETED: 11/23/01

Revised: 12/10/01

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Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 4
2. ANDA # 76-041 [**Isotretinoin Capsules USP, 10 mg, 20 mg, and 40 mg**]
3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East, Princeton, NJ 08540
Telephone: (609) 720-5612 (direct line); FAX: (609) 720-1155

Note:

The Headquarters of Ranbaxy Laboratories Limited is located at Section -18, UDYOG VIHAR INDUSTRIAL AREA, Gurgaon-122001, India

4. LEGAL BASIS FOR SUBMISSION
The innovator's U.S. Patent No. 4,464,394 expired on August 7, 2001. No marketing exclusivities have been granted to this drug product.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME _____
7. NONPROPRIETARY NAME Isotretinoin Capsules USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Ranbaxy:

11/30/00	Submission of ANDA (received at OGD 12/04/00)
01/10/01	Submission of FDA Form 3454
07/17/01	Submission of MINOR amendment
08/15/01	Submission of additional trade name
09/21/01	Submission of Bio amendment
10/15/01	Submission of MINOR amendment
12/04/01	Submission of Bio amendment
12/05/01	Submission of Bio amendment
12/20/01	Labeling Amendment
2/4/02	Bio and Minor Amendment (This review)
2/15/02	Additional bio and minor amendment information (NC)
4/1/02	Bio telephone Amendment
5/3/02	Labeling amendment
5/16/02	Amendment (Bio & CMC specs.), this review.

FDA:

01/09/01	Request for FDA Form 3454
01/11/01	Acknowledgment letter (acceptable for filing: 12/04/00)
05/18/01	NA letter (MINOR) (based on CR #1 by S. Liu, Ph.D.)

06/20/01 Deficiency letter to Ranbaxy
10/03/01 NA letter (MINOR) (based on CR #2 by S. Liu, Ph.D.)
1/9/02 NA letter (Minor) based on CR #3 by Shing Lu)
4/30/02 Bio review acceptable

10. PHARMACOLOGICAL CATEGORY Anti-acne agent

11. Rx or OTC Rx

12. RELATED IND/NDA/ANDA/DMFs

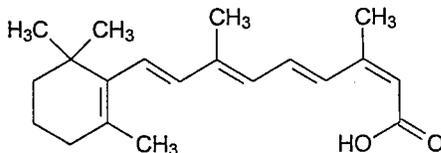
Innovator Product: Accutane® Capsules (Roche) [NDA #18-662]
10 mg and 40 mg strength: approved on 05/07/1982
20 mg strength: approved on 03/28/1983
See Item 37 for a list of DMFs referenced in the ANDA.

13. DOSAGE FORM Capsules

14. STRENGTH 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Isotretinoin. Retinoic acid, 13-*cis*-.C₂₀H₂₈O₂. 300.44. 4759-48-2.
Keratolytic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

Both Drug substance and drug product are listed in the USP 25. Bio review is acceptable and they have recommended a slight change in the future dissolution method and specification. Because of this change, the applicant is being asked to provide room temperature dissolution data for 24 month samples using the recommended method and to incorporate the changes in the method and specification in their release and stability program. Labeling review is pending. Method validation by FDA lab is not required. The EER report shows overall acceptable, even though it shows withhold for Ranbaxy Laboratories.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable (MINOR AMENDMENT)

19. REVIEWER: Ramesh Sood, Ph.D. DATE COMPLETED: May 22, 2002.

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11

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Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO. 5
2. ANDA # 76-041 [**Isotretinoin Capsules USP, 10 mg, 20 mg, and 40 mg**]
3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East, Princeton, NJ 08540
Telephone: (609) 720-5666 (direct line); FAX: (609) 720-1155

Note:

The Headquarters of Ranbaxy Laboratories Limited is located at Section -18, UDYOG VIHAR INDUSTRIAL AREA, Gurgaon-122001, India

4. LEGAL BASIS FOR SUBMISSION
The innovator's U.S. Patent No. 4,464,394 expired on August 7, 2001. No marketing exclusivities have been granted to this drug product.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME Sotret™
7. NONPROPRIETARY NAME Isotretinoin Capsules USP
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

Ranbaxy:

11/30/00	Submission of ANDA (received at OGD 12/04/00)
01/10/01	Submission of FDA Form 3454
07/17/01	Submission of MINOR amendment
08/15/01	Submission of additional trade name
09/21/01	Submission of Bio amendment
10/15/01	Submission of MINOR amendment
12/04/01	Submission of Bio amendment
12/05/01	Submission of Bio amendment
12/20/01	Labeling Amendment
2/4/02	Bio and Minor Amendment (This review)
2/15/02	Additional bio and minor amendment information (NC)
4/1/02	Bio telephone Amendment
5/3/02	Labeling amendment
5/16/02	Amendment (Bio & CMC specs.)
6/5/02	Bio amendment
7/15/02	Minor Amendment
8/5/02	Labeling Amendment
8/9/02	Labeling Amendment

11/11 02 Labeling Amendment
12/02/02 Labeling Amendment

FDA:

01/09/01 Request for FDA Form 3454
01/11/01 Acknowledgment letter (acceptable for filing: 12/04/00)
05/18/01 NA letter (MINOR) (based on CR #1 by S. Liu, Ph.D.)
06/20/01 Deficiency letter to Ranbaxy
10/03/01 NA letter (MINOR) (based on CR #2 by S. Liu, Ph.D.)
1/9/02 NA letter (Minor) based on CR #3 by Shing Lu)
4/30/02 Bio review acceptable

10. PHARMACOLOGICAL CATEGORY Anti-acne agent

11. Rx or OTC Rx

12. RELATED IND/NDA/ANDA/DMFs

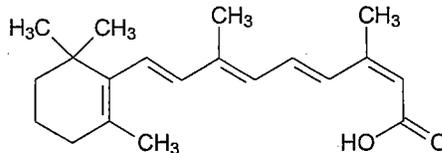
Innovator Product: Accutane® Capsules (Roche) [NDA #18-662]
10 mg and 40 mg strength: approved on 05/07/1982
20 mg strength: approved on 03/28/1983
See Item 37 for a list of DMFs referenced in the ANDA.

13. DOSAGE FORM Capsules

14. STRENGTH 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Isotretinoin. Retinoic acid, 13-*cis*-.C₂₀H₂₈O₂. 300.44. 4759-48-2.
Keratolytic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: *m. Nashed* Nashed E. Nashed, Ph.D. DATE COMPLETED: 8/1/02 *12/19/02*

Supervisor: James M. Fan: 8/9/02 *JM 12/20/02*

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RESEARCH**

APPLICATION NUMBER:

76-041

**BIOEQUIVALENCE
REVIEW(S)**

Isotretinoin Capsules USP
10 mg, 20 mg, and 40 mg
ANDA 76-041
Reviewer: F. Nouravarsani
76041SDW.N00

Ranbaxy Laboratories Limited
Gurgaon, India
Submission Date:
11/30/2000

REVIEW OF TWO BIOEQUIVALENCE STUDIES, DISSOLUTION
TESTING, AND WAIVER REQUESTS

• **Contents of Submission:**

- Bioequivalence study conducted under single-dose, fasting conditions on 40 mg Soft Gelatin Capsules
- Bioequivalence study conducted under single-dose, non-fasting conditions on 40 mg Soft Gelatin Capsules
- Dissolution testing
- Request for waivers for 10 and 20 mg Soft Gelatin Capsules.

• **The following information is found in the PDR, 2001:**

Isotretinoin is available as Accutane^R in 10 mg, 20 mg, and 40 mg soft gelatin capsules for oral administration.

Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A).

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 2.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of Accutane^R is unknown. It is indicated for the treatment of severe recalcitrant nodular acne.

Oral absorption of isotretinoin is optimal when taken with food or milk. After administration of a single 80 mg oral dose (two 40 mg capsules) of isotretinoin to 15 healthy male subjects, maximum blood concentrations ranged from 167 to 459 ng/mL (mean 256 ng/mL) and were achieved in 1 to 6 hours (mean 3.2 hours). The oral absorption of isotretinoin is consistent with first-order kinetics and can be described with a linear two-compartment model.

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. Maximum concentrations of 4-oxo-isotretinoin (87 to 399 ng/mL) were achieved at 6 to 20 hours after oral administration of two 40 mg capsules; the blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours.

Isotretinoin also undergoes isomerization to the all-trans-isomer, tretinoin, which is then metabolized to its corresponding 4-oxo-metabolite; both have been detected. Both parent compound and metabolites are further metabolized into conjugates, which are excreted.

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

The recommended dosage range for Accutane^R is 0.5 to 2 mg/kg given with food in 2 divided doses daily for 15 to 20 weeks.

BIOEQUIVALENCE STUDIES:

I. A RELATIVE BIOAVAILABILITY STUDY OF 40 MG ISOTRETINOIN SOFT GELATIN CAPSULES USP (ISOTANETM) UNDER SINGLE-DOSE, FASTING CONDITIONS (STUDY REPORT No. 001182)

STUDY OBJECTIVE:

The relative bioavailability (rate and extent of absorption) of 40 mg Isotretinoin Soft Gelatin Capsules by Ranbaxy Laboratories Limited was compared with that of 40 mg Accutane^R Soft Gelatin Capsules by Roche Laboratories following a single 80 mg oral dose in healthy male volunteers under fasting conditions.

SPONSOR: Ranbaxy Research Laboratories

STUDY FACILITY INFORMATION:

Clinical Facility: _____

Principal

Investigator: _____

Clinical Study, _____

Dosing Dates: _____

Analytical Facility: _____

Period 1: August 22, 2000

Period 2: September 12, 2000

Bioanalytical

Director: _____

Analytical Study

Between 10/10/2000 and 10/31/2000

Dates: _____

TREATMENT INFORMATION:**Treatment ID:****Test (A)****Reference (B)**

Product Name:

Isotretinoin Soft Gelatin
CapsulesAccutane^R Soft Gelatin
Capsules

Manufacturer:

Ranbaxy Laboratories Limited

Roche Laboratories

Manufacturing Date:

6/2000

N/A

Expiration Date:

5/2002

08/01

ANDA Batch Size:

_____ Capsules

N/A

Batch/Lot Number:

1077652

U0538

Strength:

40 mg

40 mg

Dosage Form:

Soft Gelatin Capsule

Soft Gelatin Capsule

Dose Administered:

80 mg (2x40 mg)

80 mg (2x40 mg)

Study Condition:

Fasting

Fasting

Length of Fasting:

Overnight before dosing
and for at least 4 hours
thereafterOvernight before dosing
and for at least 4 hours
thereafter**RANDOMIZATION:****DESIGN:**

Randomized:

Y

Design Type:

Two-Way
Crossover

No. of Sequences:

2

Replicated Treatment

N

No. of Treatments:

2

Design:

Washout Period:

21 Days

No. of Periods:

2

DOSING:**SUBJECTS:**

Single or Multiple

Single

IRB Approval:

Y

Dose:

Volume of Water

240 mL

Informed Consent

Y

Intake:

Route of

Administration:

Oral

Obtained:

No. of Subjects

40: 36 + 4

Enrolled:

No. of Subjects

alternates

Completing:

38

No. of Subjects Plasma Analyzed:	36
Sex(es) Included:	Male
Healthy Volunteers Only:	Y
Age, Years:	18-44
Height, Cm:	161-190
Weight, Kg:	61.6-89.2

Blood Sampling: 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 11, 11.5, 12, 12.5, 13, 14, 16, 24, 36, 48, 72, 96, 120 and 144 hours.

ANALYTICAL METHODOLOGY (NOT TO BE RELEASED UNDER FOI):

STATISTICAL METHODOLOGY:

Analyses of Variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, AUC_{inf}, and C_{max} using the SAS GLM procedure.

Consistent with the two one-sided test for bioequivalence, 90% confidence intervals for the difference between drug formulation LSM were calculated for the parameters AUC_{0-t}, AUC_{inf}, and C_{max} using ln-transformed data.

STUDY RESULTS:

1. CLINICAL:

- A total of 40 subjects including 4 alternates enrolled into the study.
- A total of 38 subjects completed the crossover study.
- Two subjects did not complete the study. Subjects number 21 and 32 elected to withdraw from the study for personal reasons after completion of period 1.

• **Adverse Events:**

Summary of the Post-Dose Adverse Events with a Possible Association with the Study Drug:

TEST PRODUCT (A)

Dizziness(1)

REFERENCE PRODUCT (B)

Bad aftertaste in mouth, similar to drinking Metamucil(1)

Dizziness (1)

Headache (1)

Subject stated he sees orange spots(1)

Subject stated he sees red dots(1)

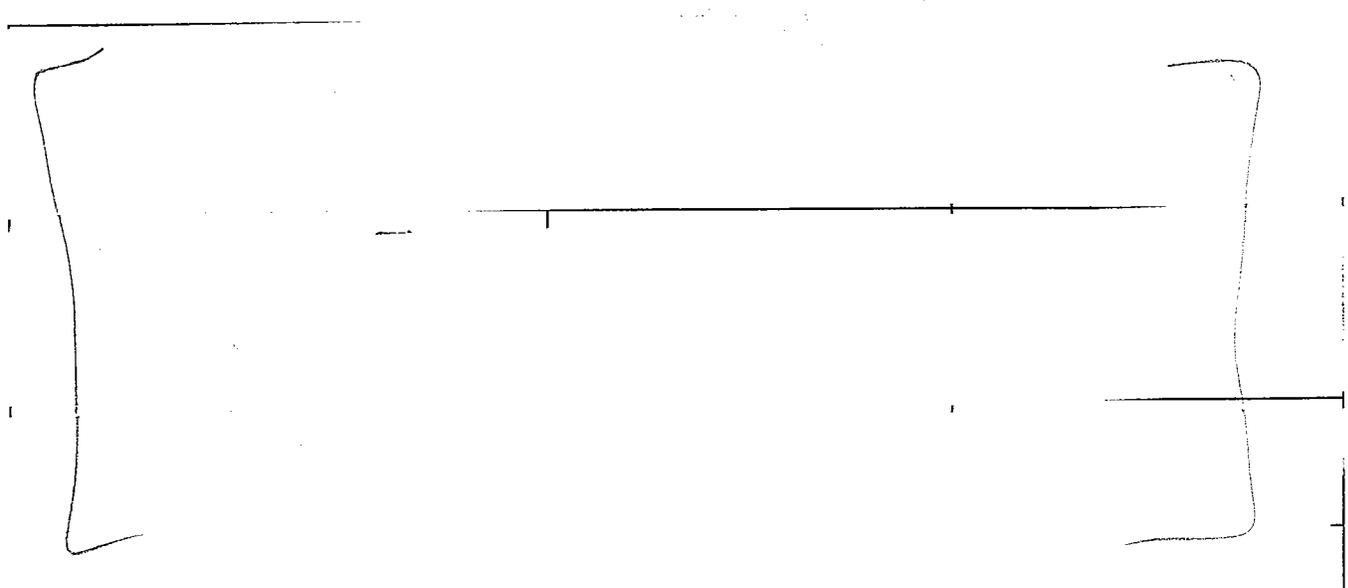
Vomiting (Unrelated to the Study Drug):

Subject No. 11 vomited (intermittently) on September 3, 2000 (unrelated to the study drug). The dose was administered on August 22, 2000 (Treatment B, Period 1).

Subject No. 24 vomited on September 17, 2000 (unrelated to the study drug). The dose was administered on September 12, 2000 (Treatment B, Period 2).

2. ANALYTICAL:

PRE-STUDY ASSAY VALIDATION FOR ISOTRETINOIN



*Analytical
method*

Redacted 1

Page(s) of trade

secret and /or

confidential

commercial

information

COMMENTS:

[]

"Inconsistent Internal Standard Response" (IISR)
"Diluted Concentration Unreliable" (DCU)
"Below Accepted Range" (BAR). The majority of the samples were reassayed due to BAR.
"Incorrect Chromatography" (IC)
"Incomplete Analysis" (IA)
"Repeat Requested by Pharmacokineticist" (RRP). Seven (7) samples were reassayed as RRP.

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ON ORIGINAL**

3. PHARMACOKINETIC/STATISTICAL ANALYSES:

ARITHMETIC MEAN (CV%) PLASMA CONCENTRATIONS (NG/ML) OF
ISOTRETINOIN VERSUS TIME, N = 36 SUBJECTS (FASTING STUDY)

TIME, HR	TEST (A)	REFERENCE (B)	RATIO% (A) / (B)
0.00	0.000 (---)	0.000 (---)	---
0.33	0.495 (374)	7.226 (229)	6.9
0.67	19.895 (167)	66.721 (137)	29.8
1.00	68.373 (125)	123.853 (100)	55.2
1.33	127.474 (93)	181.743 (80)	70.1
1.67	169.824 (76)	213.406 (73)	79.6
2.00	223.607 (66)	231.500 (73)	96.6
2.50	247.973 (56)	239.319 (62)	103.6
3.00	280.167 (54)	260.247 (51)	107.7
3.50	278.744 (52)	259.056 (45)	107.6
4.00	268.656 (49)	280.723 (39)	95.7
4.50	262.672 (47)	266.389 (45)	98.6
5.00	227.867 (46)	212.686 (43)	107.2
6.00	170.753 (43)	163.403 (37)	104.5
8.00	141.000 (81)	152.775 (90)	92.3
10.00	123.536 (77)	131.878 (83)	93.7
11.00	122.806 (73)	128.597 (80)	95.5
11.50	113.847 (64)	122.939 (76)	92.6
12.00	112.381 (67)	107.257 (44)	104.8
12.50	109.000 (60)	116.558 (71)	93.5
13.00	111.456 (70)	114.667 (75)	97.2
14.00	109.867 (78)	108.631 (74)	101.1
16.00	94.928 (71)	102.342 (83)	92.8
24.00	59.900 (65)	66.478 (86)	90.1
36.00	35.586 (56)	39.086 (65)	91.0
48.00	22.716 (50)	24.245 (55)	93.7
72.00	9.301* (51)	9.878 (66)	94.2
96.00	4.858** (75)	4.868* (86)	99.8
120.00	2.306* (129)	2.091** (161)	110.3
144.00	0.854 (258)	1.171 (255)	72.9

*: N = 35

**: N = 34

APPEARS THIS WAY
ON ORIGINAL

GEOMETRIC* Means, Ratios%, and 90% Confidence Intervals for Isotretinoin, N = 36 SUBJECTS (FASTING STUDY)

PARAMETER	MEAN		PERCENT RATIO OF MEANS (TEST/REF) *100	90% CONFIDENCE INTERVAL
	TEST	REFERENCE		
AUC _{0-t} , hr \times ng/mL	4283.05	4498.25	95.2	87.6% - 103.4%
AUC _{inf} , hr \times ng/mL	4496.88	4714.17	95.4	87.7% - 103.7%
C _{max} , ng/mL	366.84	375.33	97.7	88.8% - 107.6%

*: Geometric mean based on least squares mean of ln-transformed data

The Root Mean Square Error (Root MSE) for the ln AUC_{0-t} is 0.207886 and for ln C_{max} is 0.24177.

ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR ISOTRETINOIN, N = 36 SUBJECTS (FASTING STUDY)

PARAMETER	N	TEST		N	REFERENCE	
		TREATMENT A			TREATMENT B	
AUC _{0-t} , hr \times ng/mL	36	4571.1	(41.6)	36	4834.6	(47.7)
AUC _{inf} , hr \times ng/mL	36	4786.1	(40.3)	35	5102.5	(45.7)
C _{max} , ng/mL	36	383.03	(32.6)	36	393.778	(31.2)
T _{max} , hr	36	3.792	(65.7)	36	3.352	(48.0)
K _{el} , 1/hr	36	0.03091	(36.3)	35	0.03619	(34.4)
T _{half} , hr	36	29.0	(83.5)	35	23.43	(75.3)

The plasma concentration-time profile is found in Figure 1.

COMMENTS:

1. Statistical data analyses were performed on data from 36 subjects (Subjects number 1-20, 22-31, and 33-38).

2. The 90% confidence intervals are within the 80% and 125% limits for the ln-transformed parameters of AUC_{0-t}, AUC_{inf}, and C_{max}.

3. The data submitted for 4-oxo-isotretinoin were not reviewed, since the Division of Bioequivalence currently does not request information for 4-oxo-isotretinoin.

II. A RELATIVE BIOAVAILABILITY STUDY OF 40 MG ISOTRETINOIN SOFT GELATIN CAPSULES USP (ISOTANE™) UNDER SINGLE-DOSE, NON-FASTING CONDITIONS (STUDY REPORT NO. 001183):

STUDY OBJECTIVE:

The objective of this study was to compare the relative bioavailability of Isotretinoin Soft Gelatin Capsules, 40 mg with Accutane^R Soft Gelatin Capsules, 40 mg under fed conditions. In addition, the bioavailability of Isotretinoin Soft Gelatin Capsules, 40 mg was compared under fed and fasting conditions.

SPONSOR: Ranbaxy Research Laboratories

STUDY FACILITY INFORMATION:

Clinical Facility: _____

Principal

Investigator: _____

Clinical Study, _____

Dosing Dates: _____

Period 1: August 16, 2000

Period 2: September 06, 2000

Period 3: September 27, 2000

Analytical _____

Facility: _____

Bioanalytical _____

Director: _____

Analytical Study _____

Between 10/16/2000 and 11/08/2000

Dates: _____

TREATMENT INFORMATION:

Treatment ID:	Test (A)	Test (B)	Reference (C)
Product Name:	Isotretinoin Soft Gelatin Capsules	Isotretinoin Soft Gelatin Capsules	Accutane ^R Soft Gelatin Capsules
Manufacturer:	Ranbaxy Laboratories	Ranbaxy Laboratories	Roche Laboratories
Manufacture Date:	6/00	6/00	N/A
Expiration Date:	5/02	5/02	8/01

ANDA Batch Size:	 Capsules	 Capsules	N/A
Batch/Lot Number:	1077652	1077652	U0538
Strength:	40 mg	40 mg	40 mg
Dosage Form:	Soft Gelatin Capsules	Soft Gelatin Capsules	Soft Gelatin Capsules
Dose Administered:	80 mg (2x40 mg)	80 mg (2x40 mg)	80 mg (2x40 mg)
Study Condition:	Fasting	Fed	Fed
Length of Fasting:	Overnight	Overnight*	Overnight*
Standardized Breakfast**:	N	Y	Y

*: Overnight fast prior to the Standardized Breakfast.

** : At 30 minutes before dosing, the appropriate randomized subjects were served the following Standardized Breakfast:

One buttered English muffin
 One fried egg
 One slice of American cheese
 One slice of Canadian bacon
 One serving of hash brown potatoes
 Six fluid ounces (180 mL) of orange juice
 Eight fluid ounces (240 mL) of whole milk

RANDOMIZATION:

Randomized:	Y
No. of Sequences:	6
No. of Periods:	3
No. of Treatments:	3

DESIGN:

Design Type:	Three-Way Crossover
Replicated Treatment Design:	N
Washout Period:	21 Days

DOSING:

Single or Multiple Dose:	Single
Volume of Water Intake:	240 mL
Route of Administration:	Oral

SUBJECTS:

IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	18
No. of Subjects Completing All Three Periods:	17
No. of Subjects Plasma Analyzed:	18: 17 (3 periods); 1 (2 periods)
Sex(es) Included:	Male
Healthy Volunteers Only:	Y
Age, Years:	19 - 43
Height, Cm:	165 - 186
Weight, Kg:	60.9 - 79.2

Blood Sampling:	0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 11, 11.5, 12, 12.5, 13, 14, 16, 24, 36, 48, 72, 96, 120 and 144 hours.
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ANALYTICAL METHODOLOGY:

The same as the one reported for the fasting study.

STATISTICAL METHODOLOGY:

Analyses of variance (ANOVA) were performed on the ln-transformed AUC_{0-t}, AUC_{inf}, and C_{max} pharmacokinetic parameters using the SAS GLM procedure.

STUDY RESULTS:**1. CLINICAL:**

- Eighteen (18) subjects enrolled in the study.
- One (1) subject did not complete all study phases. Subject #15 was withdrawn from the study (**Treatment C**, Period 2: last blood draw at 144 hour) by the Medical Advisor prior to period 3 due to adverse events (Rash and itchiness on whole body, Dry skin, Bleeding cuticles of fingers on both hands, Sensitiveness at cuticles of fingers on both hands).

• Adverse Events:

Summary of the Post-Dose Adverse Events with a Probable or Possible Association with the Study Drug:

Probable**Regimen C:**

Itchiness on whole body (1)

Rash on whole body (1)

Dry skin (1)

Possible:**Regimen A:**

Headache (3)

Regimen B

Headache (2)

Dry lips (1)

Regimen C

Headache (2)

Bleeding cuticles of fingers on both hands (1)

Sensitiveness at cuticles of fingers on both hands (1)

2. ANALYTICAL:**PRE-STUDY ASSAY VALIDATION FOR ISOTRETINOIN:**

The same as the one reported for the fasting study.

**DURING STUDY ASSAY VALIDATION FOR ISOTRETINOIN
(NON-FASTING STUDY)**

PARAMETER	QUALITY CONTROL SAMPLES	STANDARD CURVE SAMPLES
		

COMMENTS:

followed).

The samples were reassayed for the following reasons:

"Inconsistent Internal Standard Response" (IISR)

"Diluted Concentration Unreliable" (DCU)
 "Incorrect Chromatography" (IC)
 "Above Accepted Range" (AAR)
 "Repeat Requested by Pharmacokineticist" (RRP).
 Seventeen (17) samples were reassayed as RRP.

3. PHARMACOKINETIC/STATISTICAL ANALYSES:

ARITHMETIC MEAN (CV%) PLASMA CONCENTRATIONS (NG/ML) OF ISOTRETINOIN, N = 18 SUBJECTS (NON-FASTING STUDY)

TIME HOUR	TEST FASTING* (A)	TEST FED (B)	REFERENCE FED (C)	RATIO% (B) / (C)
0.00	0.654 (239)	0.000 (---)	0.282 (296)	0.00
0.33	0.987 (220)	2.656 (393)	0.157 (424)	1692
0.67	25.515 (165)	39.173 (195)	0.131 (424)	29903
1.00	103.941 (104)	85.484 (134)	22.631 (391)	377.7
1.33	186.059 (69)	131.389 (117)	72.594 (259)	181.0
1.67	254.065 (52)	264.656 (98)	142.676 (198)	185.5
2.00	296.224 (41)	399.972 (79)	243.941 (156)	164.0
2.50	299.529 (43)	648.383 (67)	393.462 (114)	164.8
3.00	296.176 (45)	915.222 (58)	666.741 (75)	137.3
3.50	279.976 (44)	999.733 (52)	968.877 (61)	103.2
4.00	257.982 (41)	1060.778 (47)	1113.517 (50)	95.3
4.50	243.388 (31)	1060.833 (44)	1292.667 (41)	82.1
5.00	192.924 (33)	841.667 (46)	1044.889 (39)	80.6
6.00	148.224 (34)	593.333 (46)	760.278 (33)	78.0
8.00	127.129 (45)	431.222 (44)	568.389 (36)	75.9
10.00	108.535 (48)	336.500 (35)	432.333 (35)	77.8
11.00	102.382 (43)	310.722 (38)	396.000 (28)	78.5
11.50	102.312 (39)	300.667 (40)	384.056 (30)	78.3
12.00	97.012 (38)	293.389 (41)	362.889 (27)	80.8
12.50	97.459 (38)	281.617 (41)	352.556 (35)	79.9
13.00	94.382 (34)	269.278 (37)	340.500 (32)	79.1
14.00	91.265 (39)	253.722 (40)	312.056 (30)	81.3
16.00	82.353 (41)	221.717 (42)	285.500 (49)	77.7
24.00	53.306 (37)	137.539 (46)	155.644 (35)	88.4
36.00	33.294 (37)	68.972 (35)	75.044 (33)	91.9
48.00	20.368 (47)**	37.278 (39)	41.817 (37)	89.1
72.00	7.798 (43)	14.349 (46)	14.324 (53)	100.2
96.00	3.489 (66)***	6.094 (61)	6.328 (57)	96.3
120.00	1.444 (102)	2.940 (92)**	3.043 (67)***	96.6
144.00	0.459 (217)**	1.477 (98)	1.656 (94)*	89.2

*: N =17

**: N=16

***: N=15

**GEOMETRIC* MEANS AND RATIOS% FOR ISOTRETINOIN, N=18 SUBJECTS
(NON-FASTING STUDY)**

PARAMETER	TEST-FASTING (A)**	TEST-FED (B)	REFERENCE-FED (C)	TEST PRODUCT (FED/FAST) %	FED CONDITIONS (TEST/REF) %
AUC _{0-t} , hrxng/mL	3946.11	10997.94	12600.87	278.7	87.3
AUC _{inf} , hrxng/mL	4049.06	11111.32	12758.27	274.4	87.1
C _{max} , ng/mL	338.1206	1166.7278	1383.9095	345.1	84.3

*: Geometric mean based on least squares mean of ln-transformed data

** : N = 17

The Root Mean Square Error (Root MSE) for the ln AUC_{0-t} is 0.191732 and for ln C_{max} is 0.306191.

**ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR ISOTRETINOIN, N = 18 SUBJECTS (NON-FASTING STUDY)**

PARAMETER	N	TEST, FASTING (A)	N	TEST, FED (B)	N	REFERENCE, FED (C)
AUC _{0-t} , Hrxng/mL	17	4206.8 (28)	18	11370.6 (24)	18	12883.3 (20)
AUC _{inf} , Hrxng/mL	17	4309.3 (27)	18	11478.6 (24)	18	13030.4 (19)
C _{max} , ng/mL	17	357.4 (29)	18	1234.0 (32)	18	1456.0 (30)
T _{max} , hr	17	3.020 (50)	18	3.917 (32)	18	4.556 (32)
K _{el} , 1/hr	17	0.032886 (37)	18	0.030871 (33)	18	0.029835 (45)
T _{half} , hr	17	24.48 (47)	18	25.41 (41)	18	31.36 (82)

The plasma concentration-time profile is found in Figure 2.

COMMENTS:

1. Statistical analyses were performed on data from 18 subjects.
2. The ratios of least-squares means for Isotretinoin

In-transformed parameters AUC_{0-t}, AUC_{inf}, and C_{max} from the test product to the reference product under the fed conditions are within the range allowed for the limited food effect study.

3. The pharmacokinetic parameters AUC_{0-t}, AUC_{inf}, and C_{max} increased for the test product under the fed conditions compared with the fasting conditions.

ASSAY DATA:

PRODUCT	10 MG	20 MG	40 MG
TEST	10.19 mg Batch No.: 1077712	21.0 mg Batch No.: 1077708	39.54 mg Batch No.: 1077652
REFERENCE			40.26 mg Batch No.: U0538

CONTENT UNIFORMITY DATA (AS PERCENT OF LABEL CLAIM), MEAN (CV%), N=10:

PRODUCT	10 MG	20 MG	40 MG
TEST	99.6 (4.6) Batch No.: 1077712	99.3 (4.1) Batch No.: 1077708	105 (4.2) Batch No.: 1077652
REFERENCE	108.7 (2.1) Batch No.: U2356-50	102.3 (5.37) Batch No.: U3514-10	97.34 (3.88) Batch No.: U0538

DISSOLUTION TESTING:

- The dissolution testing was conducted using a method developed by the firm. The method and results are shown in TABLE 1.
- The dissolution testing submitted by the firm is unacceptable.
- Currently there is no FDA or USP method listed for dissolution testing of Isotretinoin Soft Gelatin Capsules.

FORMULATION COMPARISON:

Formulations of the test and reference products are shown

in TABLES 2 and 3.

The amounts of the inactive ingredients in the formulations of the test products fall in the range of the amounts listed in the FDA Inactive Ingredient Guide (January 1996) and COMIS.

WAIVER REQUEST:

The firm requested waivers of bioequivalence study requirements for its 10 mg and 20 mg strengths of Isotretinoin Soft Gelatin Capsules based on 21 CFR 320.22(d)(2). The following information was submitted by the firm:

1. Bioequivalence studies conducted under fasting and non-fasting conditions for Isotretinoin Soft Gelatin Capsules, 40 mg.
2. Dissolution testing conducted for the test and reference listed products, 10 mg, 20 mg, and 40 mg.
3. Formulations of Isotretinoin Soft Gelatin Capsules, 10, 20, and 40 mg.

The formulation of the 10 mg Isotretinoin Capsules is "exactly proportional" to the formulation of the 20 mg Isotretinoin Capsules. The inactive ingredients in formulations of 20 and 40 mg products are identical, except for Soybean Oil, USP.

DEFICIENCIES OF ANDA 76-041:

1. The dissolution testing submitted by the firm is found unacceptable by the Division of Bioequivalence. Currently there is no FDA or USP method listed for dissolution testing of isotretinoin capsules.

The firm should be informed about the following information for developing another dissolution testing method:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: 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 (a dilution factor of 2 or 5) since the analytes are found endogenously in blank plasma.

The firm should be informed for the future studies that the samples should be diluted with blank plasma.

3. The Division of Bioequivalence requests a single-dose, fasting, two-way crossover bioequivalence study comparing the test product, Isotretinoin Capsules, 20 mg with the listed reference product, Accutane^R Capsules, 20 mg by Roche Laboratories.

4. The firm may request a waiver of bioequivalence study requirements for its 10 mg isotretinoin capsules based on 21 CFR 320.22(d)(2).

RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, 40 mg (batch #1077652) comparing it to Accutane^R Capsules, 40 mg (lot #U0538) by Roche Laboratories is found acceptable by the Division of Bioequivalence.

2. The single dose, non-fasting bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, 40 mg (batch #1077652) comparing it to Accutane^R Capsules, 40 mg (lot #U0538) by Roche Laboratories is found acceptable by the Division of Bioequivalence.

3. The dissolution testing submitted by Ranbaxy Laboratories Limited on its 10, 20, and 40 mg Isotretinoin Capsules comparing them with 10, 20, and 40 mg Accutane^R Capsules by Roche Laboratories is found unacceptable by the Division of Bioequivalence.

**APPEARS THIS WAY
ON ORIGINAL**

4. The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, 6/08/2001

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

BMU 6/7/01

RD INITIALED B. Davit

FT INITIALED B. Davit

Barbara Davit

Date 6/8/01

Concur:

Dale P. Conner

Date 6/14/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

F. Nouravarsani/Draft: 05-31-2001/76041SDW.N00

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TABLE 1:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method: Proposed by the firm
Analyte: _____
Dosage Form and Strengths: Soft Gelatin Capsules
 10 mg, 20 mg, and 40 mg
No. of Units Tested: 12 Capsules
Medium: _____
Volume: _____
Apparatus: _____
RPM: _____
Assay Method: _____
Proposed Specifications: NLT (Q) of the labeled amount of
 Isotretinoin is dissolved in 60 minutes

Results:

Time, Minutes	%Dissolved		Reference Product	
	Mean%	Range%	Mean%	Range%
	Test Product 10 mg Batch #: 1077712		Reference Product 10 mg Lot No.: U2356-50 Exp. Date: 8/01	
15	96.6	_____	90.0	_____
30	99.9	_____	97.0	_____
45	102.8	_____	100.0	_____
60	104.5	_____	104.0	_____

Time, Minutes	%Dissolved		Reference Product	
	Mean%	Range%	Mean%	Range%
	Test Product 20 mg Batch #: 1077708		Reference Product 20 mg Lot No.: U3514-10 Exp. Date: 01/01	
15	78.3	_____	89.0	_____
30	99.8	_____	104.0	_____
45	101.5	_____	105.0	_____
60	102.7	_____	101.0	_____

%Dissolved

Time, Minutes	Test Product		Reference Product	
	Mean%	Range%	Mean%	Range%
	40 mg		40 mg	
	Batch #: 1077652		Lot No.: U0538	
			Exp. Date: 08/01	
15	66.0		78.0	
30	98.7		98.0	
45	102.0		104.0	
60	102.8		107.0	

TABLE 2:

FORMULATION COMPARISON OF THE TEST PRODUCTS (NOT TO BE RELEASED UNDER FOI)

INGREDIENT	STRENGTH	STRENGTH	STRENGTH
	10 MG MG/CAPSULE (%)	20 MG MG/CAPSULE (%)	40 MG MG/CAPSULE (%)
Isotretinoin, USP*	[]]
Hydrogenated Soybean Oil, NF			
Hydrogenated Vegetable Oil, NF			
White Wax, NF			
Edetate Disodium USP			
Butylated Hydroxyanisole, NF			
Soybean Oil, USP***			
Total	160.0 (100%)	320.0 (100%)	320.0 (100%)

[]

maintain a constant fill weight

TABLE 3:

FORMULATION COMPARISON OF THE REFERENCE* PRODUCTS (NOT TO BE RELEASED UNDER FOI):

INGREDIENT	STRENGTH 10.0 MG MG/CAPSULE	STRENGTH 20.0 MG MG/CAPSULE	STRENGTH 40.0 MG MG/CAPSULE
Isotretinoin	10.0	20.0	40.0**
Soybean Oil			
Beeswax			
Soybean Oil, Hydrogenated			
Vegetable Oil, Hydrogenated			
Edetate Sodium			
Butylated Hydroxyanisole			
Gelatin			
Glycerin			
Methylparaben			
Propylparaben			
Ferric Oxide Red			
Titanium Dioxide			
Dye FDC RED #3			
Dye FDC Blue #1			
Dye FDC Yellow #6			
Dye DC Yellow #10			

*: From COMIS

** : 42 mg/Capsule, a (from review of ANDA 18-662, July 16, 1981)

SUMMARY OF THE CURRENT SUBMISSIONS FOR ISOTRETINOIN SOFT GELATIN CAPSULES:

<u>Submission</u>	<u>Firm</u>	<u>Date</u>	<u>Study</u>	<u>Decision</u>
ANDA 75-945	Genpharm	08/21/00	STF	AC
			STP	AC
			DIS	UA
			DIW	IC

There is no acceptable method for dissolution testing of isotretinoin capsules. The firm was encouraged to develop another method and specification using the following information:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

CD 01-023 ~~XXXXXXXXXXXX~~ 01/08/01
~~XXXXXXXXXXXX~~

- Analysis of only isotretinoin (parent drug) is sufficient in bioequivalence studies of a generic isotretinoin capsule. There is no evidence suggesting that 4-oxo-isotretinoin is formed by pre-systemic metabolism or contributes meaningfully to the safety and/or efficacy of the drug.
- The Division of Bioequivalence requests the following bioequivalence studies for the generic isotretinoin capsules:
 1. A single-dose, two-way crossover study under fasting conditions on the 40 mg strength.
 2. A single-dose, two-way crossover study under fed conditions on the 40 mg strength.
 3. A single-dose, two-way crossover study under fasting conditions on the 20 mg strength.
- An in vivo bioequivalence determination on the 10 mg strength of isotretinoin capsules can be waived based on formulation proportionality of the active and inactive ingredients and dissolution profile comparisons between the strengths used in the in vivo studies.
- The DBE requests that comparative in vitro dissolution testing be conducted on 12 dosage units of each strength of the proposed isotretinoin capsules and Accutane^R capsules. At present there is no FDA or USP method for dissolution testing of isotretinoin capsules. The firm is encouraged to develop its own method and specification using the following information:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

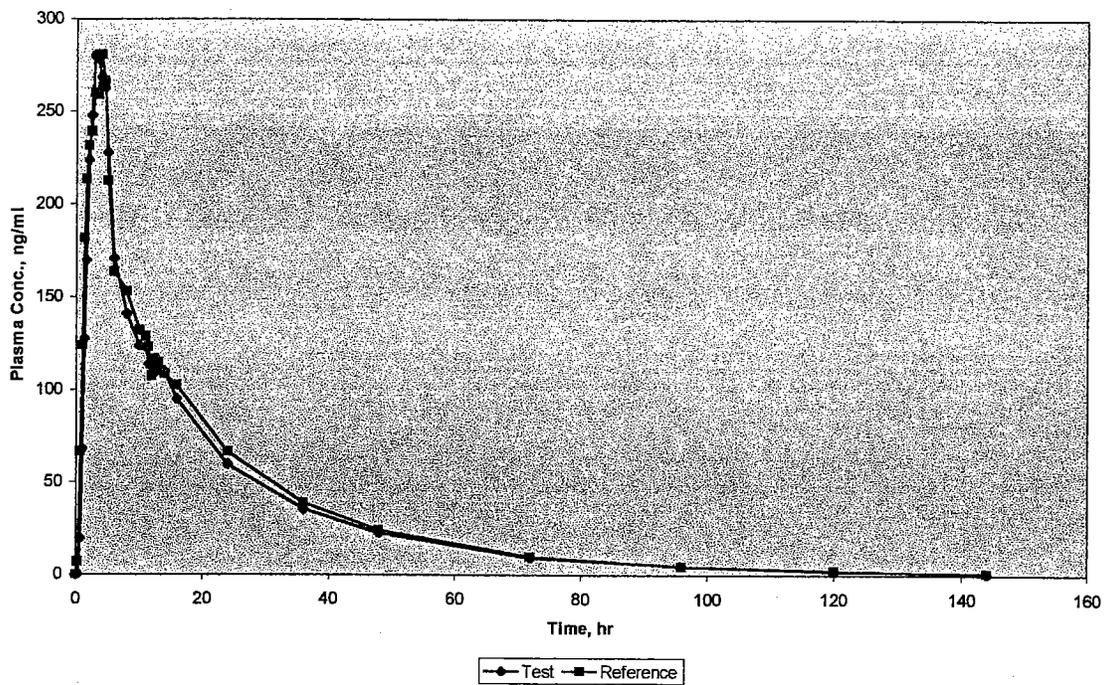
ANDA 76-135	Barr	03/20/01	STF	AC
			STP	AC
			DIS	UA

STF: Single-Dose/Fasting
STP: Single-Dose/Fed
DIS: Dissolution
DIW: Dissolution/Waiver

AC: Acceptable
UA: Unacceptable
IC: Incomplete

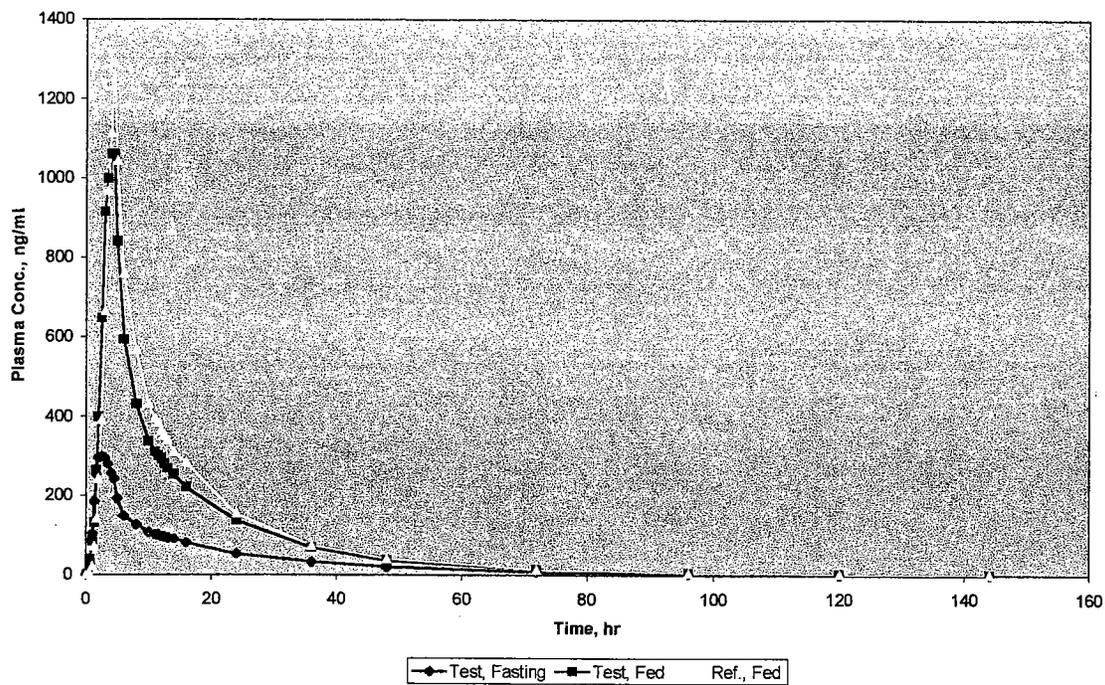
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Figure 1: Mean Plasma Isotretinoin Concentrations



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Figure 2: Mean Plasma Isotretinoin Concentrations



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BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-041

APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCTS:

Isotretinoin Capsules USP
10 mg, 20 mg, and 40 mg

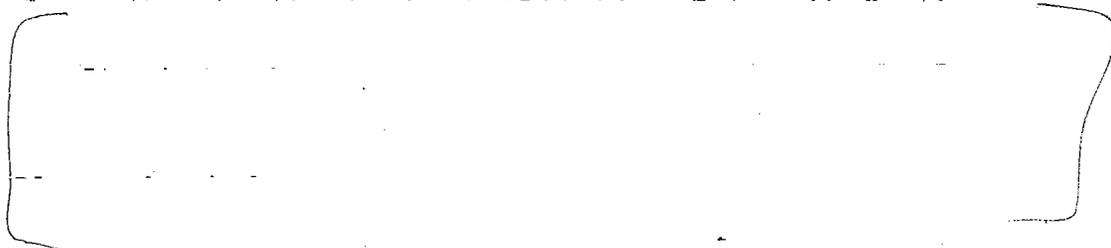
The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your method of dissolution testing is unacceptable to the Division of Bioequivalence. The following information may be used for developing another dissolution testing method:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

2.



3. The Division of Bioequivalence requests a single-dose, fasting, two-way crossover bioequivalence study comparing the test product, Isotretinoin Capsules, 20 mg with the listed reference product, Accutane^R Capsules, 20 mg by Roche Laboratories.

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4. You may request a waiver of bioequivalence study requirements for the 10 mg isotretinoin capsules based on formulation proportionality to the 20 mg capsule, acceptable bioequivalence study conducted on the 20 mg capsules, and acceptable dissolution testing.

Sincerely yours,

fn 

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

**APPEARS THIS WAY
ON ORIGINAL**

CC: ANDA 76-041
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-658/F. Nouravarsani

V:\FIRMSNZ\Ranbaxy\ltrs&rev\76041SDW.N00

Printed in final on 6/08/2001

Endorsements: (Final with Dates)

HFD-658/F. Nouravarsani, Farafing Nouravarsani, 6/08/2001
HFD-658/B. Davit, Babbar M. Davit 6/8/01
HFD-650/D. Conner for lup 6/14/2001

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATE:

11/30/2000

OK 1. Fasting Study (STF)

Strength: 40 mg Capsules

Clinical: _____

Outcome: AC

Analytical: _____

OK 2. Food Study (STP)

Strength: 40 mg Capsules

Clinical: _____

Outcome: AC

Analytical: _____

OK 3. DISSOLUTION WAIVER (DIW)

Strength: 10 mg Capsules

Outcome: IC

OK 4. DISSOLUTION WAIVER (DIW)

Strength: 20 mg Capsules

Outcome: IC

Outcome Decision: IC

WinBio Comments: Bio-studies were found acceptable.
Dissolution testing was found unacceptable.
Waivers were not granted.

Isotretinoin Capsules USP
10 mg, 20 mg, and 40 mg
ANDA 76-041
Reviewer: F. Nouravarsani
76041STA.901

Ranbaxy Laboratories Limited
Gurgaon, Haryana, India
Submission Date:
9/21/2001

**REVIEW OF A STUDY AMENDMENT: BIOEQUIVALENCE STUDY,
DISSOLUTION TESTING, AND WAIVER REQUEST**

I. INTRODUCTION:

- Ranbaxy Laboratories Limited had previously submitted the following studies (Submission Letter Date: 11/30/2000):
 - Bioequivalence study conducted under single-dose, fasting conditions on 40 mg Soft Gelatin Capsules
 - Bioequivalence study conducted under single-dose, non-fasting conditions on 40 mg Soft Gelatin Capsules
 - Dissolution testing
 - Request for waivers for 10 and 20 mg Soft Gelatin Capsules.

The above bioequivalence studies were found acceptable.

The dissolution testing was found incomplete.

• **Contents of the Current Submission:**

- Responses to the deficiencies of the submission dated 11/30/00.
 - Bioequivalence study conducted under single-dose, fasting conditions on 20 mg Soft Gelatin Capsules
 - Dissolution testing
 - Request for waiver for 10 mg Soft Gelatin Capsules.
- **The following information is found in the PDR, 2001:**

Isotretinoin is available as Accutane^R in 10 mg, 20 mg, and 40 mg soft gelatin capsules for oral administration. Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 2.0 mg/kg/day, inhibits

sebaceous gland function and keratinization. The exact mechanism of action of Accutane^R is unknown. It is indicated for the treatment of severe recalcitrant nodular acne.

Oral absorption of isotretinoin is optimal when taken with food or milk. After administration of a single 80 mg oral dose (two 40 mg capsules) of isotretinoin to 15 healthy male subjects, maximum blood concentrations ranged from 167 to 459 ng/mL (mean 256 ng/mL) and were achieved in 1 to 6 hours (mean 3.2 hours). The oral absorption of isotretinoin is consistent with first-order kinetics and can be described with a linear two-compartment model. 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. Maximum concentrations of 4-oxo-isotretinoin (87 to 399 ng/mL) were achieved at 6 to 20 hours after oral administration of two 40 mg capsules; the blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours.

Isotretinoin also undergoes isomerization to the all-trans-isomer, tretinoin, which is then metabolized to its corresponding 4-oxo-metabolite; both have been detected. Both parent compound and metabolites are further metabolized into conjugates, which are excreted.

Following administration of an 80 mg liquid suspension oral dose of ¹⁴C-isotretinoin, ¹⁴C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). The terminal elimination half-life of isotretinoin ranges from 10 to 20 hours. The mean elimination half-life of 4-oxo-isotretinoin is 25 hours (range 17 to 50 hours).

The recommended dosage range for Accutane^R is 0.5 to 2 mg/kg given with food in 2 divided doses daily for 15 to 20 weeks.

II. DEFICIENCIES AND RESPONSES (AMENDMENT DATED 9/21/2001):**DEFICIENCY #1:**

The dissolution testing submitted by the firm was found unacceptable by the Division of Bioequivalence. The firm was informed about the following information for developing another dissolution testing method:

Stimuli Article: Pharmacopoeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

RESPONSE #1:**• Dissolution Media:**

- During the dissolution method development studies, one batch of each test product and reference product (40 mg strength) was studied in different dissolution media (Table 1).
- The cumulative percent of Isotretinoin dissolved was very low for both the test and reference products in all media except for _____ (Table 1).
- The firm states that "Based on the in-house dissolution testing data in different media and the references from Pharmacopoeial Forum (PF) and British Pharmacopoeia (BP), it was concluded to use _____ as dissolution media (medium) for Isotretinoin capsules."
- The firm further states that "We note and acknowledge that one of the reasons for not adopting the proposed PF dissolution method in the USP monograph is that the media (medium) has a high pH. However, since there is practically no release of drug in any other media, there is no choice left but to use _____ as the dissolution media (medium)."

- **Dissolution Apparatus:**

- Dissolution testing with various speed of the _____ was conducted to evaluate the optimum rotational speed (rpm) of the apparatus for the dissolution of the products (Table 2).
- The firm states that "release of drug from the reference product was incomplete at _____ However, when the test was run with _____ paddle speed, complete drug release was obtained for both test and reference products in 60 minutes."

- **Additional Studies:**

Additional dissolution data were also submitted for all strengths of the test and reference products using, _____

- **Conclusion:**

The firm proposes to use the same method that was submitted in the original ANDA 76-041 (Table 3).

COMMENTS:

1. The dissolution testing method (Table 3) proposed by the firm is unacceptable.
2. Currently there is no FDA or USP method listed for the dissolution testing of Isotretinoin Soft Gelatin Capsules.

DEFICIENCY #2:

RESPONSE #2:

The firm responded that "We note and acknowledge the Agency's comment."

DEFICIENCY #3:

The Division of Bioequivalence requested a single-dose, fasting, two-way crossover bioequivalence study comparing the test product, Isotretinoin Capsules, 20 mg with the listed reference product, Accutane^R Capsules, **20 mg** by Roche Laboratories.

RESPONSE #3:

The firm submitted a bioequivalence study conducted under single-dose, fasting conditions on **20 mg** Soft Gelatin Capsules in its current submission.

BIOEQUIVALENCE STUDY (STUDY No. 011748):**STUDY OBJECTIVE:**

The relative bioavailability (rate and extent of absorption) of 20 mg Isotretinoin Soft Gelatin Capsules by Ranbaxy Laboratories Limited was compared with that of 20 mg Accutane^R Soft Gelatin Capsules by Roche Laboratories following a single 80 mg oral dose in healthy male volunteers under fasting conditions.

SPONSOR: Ranbaxy Research Laboratories

STUDY FACILITY INFORMATION:

Clinical Facility: _____

Principal

Investigator: _____

Clinical Study,

Period 1: July 12, 2001

Dosing Dates:

Period 2: August 02, 2001

Analytical Facility: _____

Bioanalytical

Director: _____

Analytical Study

From 8/15/2001 and 8/30/2001

Dates:

TREATMENT INFORMATION:

Treatment ID:

Test (A)

Reference (B)

Product Name:

Isotretinoin Soft Gelatin Capsules

Accutane^R Soft Gelatin Capsules

Manufacturer:

Ranbaxy Laboratories Limited

Roche Laboratories

Manufacturing Date:

6/2000*

N/A

Expiration Date:

5/2002

09/2002

ANDA Batch Size:

_____ Capsules**

N/A

Batch/Lot Number:	1077708	U3584
Strength:	20 mg	20 mg
Dosage Form:	Soft Gelatin Capsule	Soft Gelatin Capsule
Dose Administered:	80 mg (4x20 mg)	80 mg (4x20 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight before dosing and for at least 4 hours thereafter	Overnight before dosing and for at least 4 hours thereafter

*: Volume 1.11, page 2996

** : Volume 1.11, page 2995

RANDOMIZATION:

Randomized:	Y
No. of Sequences:	2
No. of Treatments:	2
No. of Periods:	2

DESIGN:

Design Type:	Two-Way Crossover
Replicated Treatment Design:	N
Washout Period:	21 Days

DOSING:

Single or Multiple Dose:	Single
Volume of Water Intake:	240 mL
Route of Administration:	Oral

SUBJECTS:

IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	40: 36 + 4 alternates
No. of Subjects Completed:	39
No. of Subjects Plasma Analyzed:	36
Sex(es) Included: Healthy Volunteers Only:	Male Y
Age, Years:	18-45 Mean 32.3
Height, Cm:	168-189 Mean 176.1
Weight, Kg:	61.9-91.0 Mean 75.78
Race:	Caucasian 39 Black 1

BLOOD SAMPLING:

0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5,
4, 4.5, 5, 6, 8, 10, 11, 11.5, 12, 12.5, 13,
14, 16, 24, 36, 48, 72, 96, 120, and 144 hours.

ANALYTICAL METHODOLOGY (NOT TO BE RELEASED UNDER FOI):

Analytes: _____
Assay Method: _____
Matrix: _____
Internal Standard: _____

STATISTICAL METHODOLOGY:

Analyses of Variance (ANOVA) were performed on the ln-transformed AUC0-t, AUCinf, and Cmax using the SAS GLM procedure.

The 90% confidence interval calculations were based on the LSM values generated by the SAS LSMEANS option to the SAS GLM procedure and the standard error of the estimate as given by the GLM procedure.

STUDY RESULTS:

1. CLINICAL:

- A total of 40 subjects including 4 alternates enrolled into the study.
- A total of 39 subjects completed the clinical phase of the study. Subject number 20 withdrew from the study for personal reasons following his pre-dose blood draw in period 2.

• Adverse Events:

No serious adverse events were reported during the study.

Summary of the Post-Dose Adverse Events with a Probable or Possible Association with the Study Drug:

Adverse Event	Treatment	Subject	Relationship To Treatment
Headache	A	4	Pos
	A	9	Pos
	A	33	Pos
	B	4	Pos
	B	29	Pos
	B	33	Pos
Feels exhausted	A	4	Pos
Loss of appetite	A	4	Pos

Nausea	A	4	Pos
	A	9	Pos
	B	4	Pos
	B	29	Pos
Eyes are sensitive to the light	A	9	Pro
Dizziness	A	9	Pos
Vomited (1.2 days after dosing)	A	9	Pos
Vomited (2.6 days after dosing)	B	4	Pos
Burning sensation in eyes	A	24	Pro
Dry mouth	A	33	Pos
Fingertips are dry on both hands	B	3	Pos
Lips on interior portion of mouth have dry skin	B	3	Pos
Trembling in left arm	B	9	Pos
Itchiness on face and body (chest area)	B	32	Pos
Loose stool	B	32	Pos
Both eyes feel dry	B	33	Pro
Burning sensation in both eyes	B	33	Pro
Nose feels dry (inside)	B	33	Pro

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Page(s) of trade

secret and /or

confidential

commercial

information

DURING STUDY ASSAY VALIDATION FOR ISOTRETINOIN
(FASTING STUDY)

PARAMETER	QUALITY CONTROL SAMPLES	STANDARD CURVE SAMPLES
[] _____ _____

COMMENTS:

[

"Inconsistent Internal Standard Response" (IISR)
"Diluted Concentration Unreliable" (DCU)
"Incomplete Analysis" (IA)
"Pharmacokinetic Repeats" (PK): Three samples were
reassayed. However, their original values were reported.

[

acceptable for this submission since the results of those

quality control samples, which were diluted along with the "study samples" are similar to those that were not diluted. Furthermore, the majority of the samples were undiluted.

3. PHARMACOKINETIC/STATISTICAL ANALYSES:

ARITHMETIC MEAN (CV%) PLASMA CONCENTRATIONS (NG/ML) OF ISOTRETINOIN VERSUS TIME, N = 36 SUBJECTS (FASTING STUDY)

TIME, HR	TEST (A)	REFERENCE (B)	RATIO% (A) / (B)
0.00	0.000 (---)	0.000 (---)	---
0.33	0.382 (366)	3.651 (170)	0.105
0.67	27.996 (211)	89.101 (115)	0.314
1.00	95.484 (121)	191.196 (75)	0.499
1.33	169.595 (85)	287.622 (59)	0.590
1.67	255.614 (65)	328.372 (53)	0.778
2.00	332.872 (53)	368.773 (52)	0.903
2.50	375.325 (46)	370.889 (41)	1.012
3.00	366.508 (42)	377.111 (36)	0.972
3.50	361.414 (41)	343.806 (34)	1.051
4.00	330.811 (39)	324.111 (34)	1.021
4.50	321.092 (39)	281.861 (39)	1.139
5.00	239.058 (35)	219.250 (36)	1.090
6.00	180.233 (33)	173.894 (34)	1.036
8.00	136.456 (36)	131.828 (32)	1.035
10.00	119.911 (33)	116.592 (27)	1.028
11.00	115.889 (32)	112.414 (27)	1.031
11.50	114.583 (32)	110.689 (27)	1.035
12.00	109.300 (30)	108.411 (28)	1.008
12.50	105.025 (32)	102.872 (28)	1.021
13.00	102.675 (31)	100.397 (27)	1.023
14.00	95.278 (31)	91.866* (28)	1.037
16.00	84.361 (33)	80.422 (25)	1.049
24.00	54.675 (29)	51.589 (28)	1.060
36.00	34.934* (42)	31.811* (33)	1.098
48.00	20.286* (44)	19.595 (43)	1.035
72.00	8.660* (67)	8.092& (71)	1.070
96.00	3.839** (123)	3.605* (123)	1.065
120.00	2.008 (200)	1.977 (196)	1.016
144.00	0.706 (371)	1.136 (299)	0.621

*: N = 35

** : N = 34

& : N = 33

The plasma concentration-time profile is found in Figure 1.

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GEOMETRIC* MEANS, RATIOS%, AND 90% CONFIDENCE INTERVALS FOR ISOTRETINOIN, N = 36 SUBJECTS (FASTING STUDY)

PARAMETER	MEAN		PERCENT RATIO OF MEANS (TEST/REF) *100	90% CONFIDENCE INTERVAL
	TEST	REFERENCE		
AUC _{0-t} , hr \times ng/mL	4370.10	4420.98	98.8	89.3% - 109.4%
AUC _{inf} , hr \times ng/mL	4515.57	4570.88	98.8	90.0% - 108.4%
C _{max} , ng/mL	438.7855	465.6275	94.2	82.8% - 107.2%

*: Geometric mean based on least squares mean of ln-transformed data

The Root Mean Square Error (Root MSE) for the ln AUC_{0-t} is 0.254934 and for ln C_{max} is 0.323720.

ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR ISOTRETINOIN (FASTING STUDY)

PARAMETER	N	TEST		N	REFERENCE	
		TREATMENT A			TREATMENT B	
AUC _{0-t} , hr \times ng/mL	36	4630.4	(30.0)	36	4570.2	(27.4)
AUC _{inf} , hr \times ng/mL	36	4772.3	(31.1)	36	4740.4	(29.2)
C _{max} , ng/mL	36	465.97	(29.3)	36	479.53	(26.9)
T _{max} , hr	36	2.880	(35.9)	36	2.407	(43.8)
K _{el} , 1/hr	36	0.039908	(35.2)	36	0.03953	(38.8)
T _{half} , hr	36	21.032	(61.9)	36	21.872	(62.8)

COMMENTS:

1. Statistical data analyses were performed on data from 36 subjects (Subjects number 1-19, 21-36, and 38).
2. The 90% confidence intervals are within the 80% and 125% limits for the ln-transformed parameters of AUC_{0-t}, AUC_{inf}, and C_{max}.

3. The data submitted for 4-oxo-isotretinoin were not reviewed, since the Division of Bioequivalence currently does not request information for 4-oxo-isotretinoin.

ASSAY DATA:

PRODUCT	10 MG	20 MG	40 MG
TEST	10.19 mg Batch No.: 1077712 Batch Size: Capsules Manufacturing Date: June 2000	21.0 mg Batch No.: 1077708 Batch Size: Capsules Manufacturing Date: June 2000	39.54 mg Batch No.: 1077652 Batch Size: Capsules Manufacturing Date: June 2000
REFERENCE	---	---	40.26 mg Batch No.: U0538

CONTENT UNIFORMITY DATA (AS PERCENT OF LABEL CLAIM), MEAN (CV%), N=10:

PRODUCT	10 MG	20 MG	40 MG
TEST	99.6 (4.6) Batch No.: 1077712	99.3 (4.1) Batch No.: 1077708	105 (4.2) Batch No.: 1077652
REFERENCE	108.7 (2.1) Batch No.: U2356-50	102.3 (5.37) Batch No.: U3514-10	97.34 (3.88) Batch No.: U0538

FORMULATION COMPARISON:

Formulations of the test products are shown in Table 4.

The amounts of the inactive ingredients in the formulations of the test products fall in the range of the amounts listed in the FDA Inactive Ingredient Guide (January 1996) and COMIS.

WAIVER REQUEST:

The firm requested waiver of bioequivalence study requirements for its 10 mg Isotretinoin Soft Gelatin

Capsules based on 21 CFR 320.22(d)(2). The following information was submitted by the firm:

1. Bioequivalence studies conducted under fasting and non-fasting conditions for Isotretinoin Soft Gelatin Capsules, 40 mg.
2. Bioequivalence study conducted under fasting conditions for Isotretinoin Soft Gelatin Capsules, 20 mg.
3. Dissolution testing conducted for the test and reference listed products, 10 mg, 20 mg, and 40 mg.
4. Formulations of Isotretinoin Soft Gelatin Capsules, 10, 20, and 40 mg.

The formulation of the 10 mg Isotretinoin Capsules is "exactly proportional" to the formulation of the 20 mg Isotretinoin Capsules. The inactive ingredients in formulations of 20 and 40 mg products are identical, except for _____

III. DEFICIENCIES OF THE CURRENT SUBMISSION:

1. Assayed potency data should be submitted for the reference product, Accutane^R Capsules, 20 mg (lot #U3584).
2. The dissolution testing submitted by the firm is found unacceptable by the Division of Bioequivalence.

The Division of Bioequivalence requests submission of dissolution testing data using _____

_____ with an optimum rotation speed (not to exceed _____). The sampling times should be at 20, 40, 60, 90, and 120 minutes.

IV. RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, 20 mg (batch #1077708) comparing it to Accutane^R Capsules, 20 mg (lot #U3584) by Roche Laboratories is found incomplete by the Division of Bioequivalence.
2. The dissolution testing submitted by Ranbaxy

Laboratories Limited on its 10, 20, and 40 mg Isotretinoin Capsules comparing them with 10, 20, and 40 mg Accutane^R Capsules by Roche Laboratories is found unacceptable by the Division of Bioequivalence.

3. The waiver of bioequivalence study requirements for Isotretinoin Soft Gelatin Capsules, 10 mg is not granted.

4. The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, 10/31/2001

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

BMD 10/31/01

RD INITIALED B. Davit
FT INITIALED B. Davit

Barbara M Davit Date *10/31/01*

Concur:

Dale P. Conner
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date *10/31/01*

F. Nouravarsani/Draft: 10-26-2001/76041STA.901

TABLE 1:**DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)**

Analyte: _____
 Dosage Form and Strength: Soft Gelatin Capsules, 40 mg
 Volume: _____
 Apparatus: _____
 RPM: _____

RESULTS:**CUMULATIVE PERCENT OF ISOTRETINOIN DISSOLVED:**

Dissolution Medium	Test Product, 40 mg				Reference Product, 40 mg			
	Lot #: IDR5(665)08				Lot No.: 0499			
	Exp. Date: 1/01				Exp. Date: 7/00			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 2:**DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)**

Analyte: _____
 Dosage Form and Strength: Soft Gelatin Capsules, 40 mg
 Medium: _____
 Volume: _____
 Apparatus: _____
 RPM: _____

RESULTS:**CUMULATIVE PERCENT OF ISOTRETINOIN DISSOLVED:**

Rotation Speed	Test Product, 40 mg				Reference Product, 40 mg			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
	Lot #: IDR5(665)08				Lot No.: 0499			
	Exp. Date: 1/01				Exp. Date: 7/00			

APPEARS THIS WAY
ON ORIGINAL

TABLE 3:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method: Proposed by the firm
Analyte: _____
Dosage Form and Strengths: Soft Gelatin Capsules
 10 mg, 20 mg, and 40 mg
No. of Units Tested: 12 Capsules
Medium: _____
Volume: _____
Apparatus: _____
RPM: _____
Assay Method: _____
Proposed Specifications: NLT _____(Q) of the labeled amount of
 Isotretinoin is dissolved in 60 minutes

Results:

Time, Minutes	%Dissolved		Reference Product	
	Mean%	Range%	Mean%	Range%
	Test Product		Reference Product	
	10 mg		10 mg	
	Batch #: 1077712		Lot No.: U2356-50	
			Exp. Date: 8/01	
15	96.6	_____	90.0	_____
30	99.9	_____	97.0	_____
45	102.8	_____	100.0	_____
60	104.5	_____	104.0	_____

Time, Minutes	%Dissolved		Reference Product	
	Mean%	Range%	Mean%	Range%
	Test Product		Reference Product	
	20 mg		20 mg	
	Batch #: 1077708		Lot No.: U3514-10	
			Exp. Date: 01/01	
15	78.3	_____	89.0	_____
30	99.8	_____	104.0	_____
45	101.5	_____	105.0	_____
60	102.7	_____	101.0	_____

%Dissolved

Time, Minutes	Test Product 40 mg Batch #: 1077652	Reference Product 40 mg Lot No.: U0538 Exp. Date: 08/01
	<u>Mean%</u> <u>Range%</u>	<u>Mean%</u> <u>Range%</u>
15	66.0 	78.0
30	98.7 	98.0
45	102.0 	104.0
60	102.8 	107.0

TABLE 4:

FORMULATION COMPARISON OF THE TEST PRODUCTS (NOT TO BE RELEASED UNDER FOI)

INGREDIENT	STRENGTH 10 MG MG/CAPSULE (%)	STRENGTH 20 MG MG/CAPSULE (%)	STRENGTH 40 MG MG/CAPSULE (%)
Isotretinoin, USP*	<div style="border: 1px solid black; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> [</div>	<div style="border: 1px solid black; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;">] </div>	<div style="border: 1px solid black; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;">] </div>
Hydrogenated Soybean Oil, NF			
Hydrogenated Vegetable Oil, NF			
White Wax, NF			
Edetate Disodium USP			
Butylated Hydroxyanisole, NF			
Soybean Oil, USP***			
Total	160.0 (100%)	320.0 (100%)	320.0 (100%)

[

SUMMARY OF THE CURRENT SUBMISSIONS FOR ISOTRETINOIN SOFT GELATIN CAPSULES:

Submission	Firm	Date	Study	Decision
ANDA 75-945	Genpharm	08/21/00	STF, 40 mg	AC
			STP, 40 mg	AC
			DIS	UA
			DIW, 10 mg	IC
			DIW, 20 mg	IC

There is no acceptable method for dissolution testing of isotretinoin capsules. The firm was encouraged to develop another method and specification using the following information:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

ANDA 75-945	Genpharm	03/21/01	STA:	
		And	DIS	AC
		06/14/01	STF, 10 mg	AC
			DIW, 20 mg	AC

COMMENT:

"The dissolution method developed by the firm is acceptable as an interim dissolution method until the USP dissolution method is published. The dissolution testing should be conducted using the following method:

Apparatus: _____

Agitation: _____

Medium: _____

No. Units Tested: 12
 Reference Drug: Accutane
 Analytical Method: _____
 Tolerance (Q): NLT — in 90 minutes"

CD 01-023 _____ 01/08/01

- Analysis of only isotretinoin (parent drug) is sufficient in bioequivalence studies of a generic isotretinoin capsule. There is no evidence suggesting that 4-oxo-isotretinoin is formed by pre-systemic metabolism or contributes meaningfully to the safety and/or efficacy of the drug.
- The Division of Bioequivalence requests the following bioequivalence studies for the generic isotretinoin capsules:
 1. A single-dose, two-way crossover study under fasting conditions on the 40 mg strength.

2. A single-dose, two-way crossover study under fed conditions on the 40 mg strength.
 3. A single-dose, two-way crossover study under fasting conditions on the 20 mg strength.
- An in vivo bioequivalence determination on the 10 mg strength of isotretinoin capsules can be waived based on formulation proportionality of the active and inactive ingredients and dissolution profile comparisons between the strengths used in the in vivo studies.
 - The DBE requests that comparative in vitro dissolution testing be conducted on 12 dosage units of each strength of the proposed isotretinoin capsules and Accutane^R capsules. At present there is no FDA or USP method for dissolution testing of isotretinoin capsules. The firm is encouraged to develop its own method and specification using the following information:

Stimuli Article: Pharmacopeial Forum, September-October 1998, page 7045.

The FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

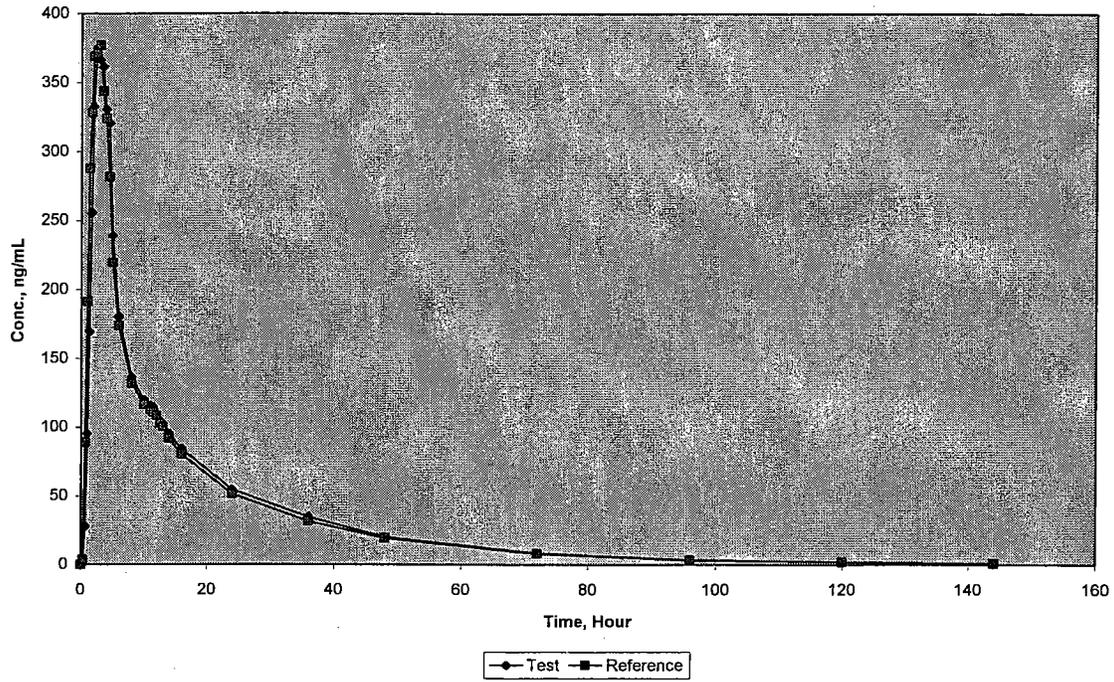
ANDA 76-135	Barr	03/20/01	STF	AC
			STP	AC
			DIS	UA
ANDA 76-041	Ranbaxy	11/30/00	STF	AC
			STP	AC
			DIS	IC
			DIW	IC
PRO 01-014	Berlex	03/01/01		

Comments:

"In a bio-management meeting (7 May 2001) it was decided that only isotretinoin be measured. Fasted and fed biostudies will need to be conducted on the 40 mg capsule. A fasted bio-study may be conducted on the 20 mg capsule (10 mg capsule eligible for waiver) or the 10 mg capsule (20 mg capsule eligible for waiver)."

STF: Single-Dose/Fasting	AC: Acceptable
STP: Single-Dose/Fed	UA: Unacceptable
DIS: Dissolution	IC: Incomplete
DIW: Dissolution/Waiver	

Figure 1: Mean Plasma Isotretinoin Concentrations



APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-041 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCTS: Isotretinoin Capsules USP
 10 mg, 20 mg, and 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit assayed potency data for the reference product, Accutane^R Capsules, 20 mg (lot #U3584).
2. Your proposed dissolution testing method is unacceptable to the Division of Bioequivalence.

Please submit dissolution testing data for the test and reference products using

_____ with an optimum rotation speed (not to exceed _____). The sampling times should be at 20, 40, 60, 90, and 120 minutes.

Sincerely yours,



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

CC: ANDA 76-041
ANDA DUPLICATE
DIVISION FILE
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HFD-658/F. Nouravarsani

V:\FIRMSNZ\Ranbaxy\ltrs&rev\76041STA.901

Printed in final on 10/31/2001

Endorsements: (Final with Dates)

HFD-658/F. Nouravarsani, Farahnaz Nouravarsani, 10/31/2001
HFD-658/B. Davit BNS 10/31/01
HFD-650/D. Conner OR 10/31/01

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATE:

09/21/2001

ok

FASTING STUDY (STF), ORIGINAL

Strength: 20 mg Capsules

Clinical: _____

OUTCOME: IC

Analytical: _____

of

STUDY AMENDMENT (STA)
(09/21/2001)

new
dissolution
data

Strengths: All

OUTCOME: IC

OUTCOME DECISION: IC

WINBIO COMMENTS:

Fasting study was found incomplete.
Dissolution testing was found unacceptable.
Waiver for 10 mg strength was not granted.

**APPEARS THIS WAY
ON ORIGINAL**

reason that the unexpired lot (U3584) for 20 mg reference product was not used for the dissolution testing.

Sincerely yours,



Dale P. Conner, Pharm.D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Isotretinoin Capsules USP
 10 mg, 20 mg, and 40 mg
 ANDA 76-041
 Reviewer: F. Nouravarsani
 76041STA.D01

Ranbaxy Laboratories Limited
 Gurgaon, India
 Submission Date:
 12/04/2001

REVIEW OF AN AMENDMENT

I. CONTENT OF THE CURRENT SUBMISSION:

Responses to the deficiencies of the submission dated 9/21/2001.

II. DEFICIENCIES AND RESPONSES:

DEFICIENCY #1:

The firm was asked to submit assayed potency data for the reference product, Accutane^R Capsules, 20 mg (lot #U3584).

RESPONSE #1:

The firm submitted the requested data. The assayed potency data are summarized as follows:

ASSAYED POTENCY DATA:

PRODUCT	10 MG CAPSULES	20 MG CAPSULES	40 MG CAPSULES
TEST	10.19 mg Batch No.: 1077712 Batch Size: <u> </u> Capsules Manufacturing Date: June 2000	21.0 mg Batch No.: 1077708 Batch Size: <u> </u> Capsules Manufacturing Date: June 2000	39.54 mg Batch No.: 1077652 Batch Size: <u> </u> Capsules Manufacturing Date: June 2000
REFERENCE	---	20.13 mg Lot #: U3584 Expiration Date: 9/2002	40.26 mg Batch No.: U0538 Expiration Date: 8/2001

DEFICIENCY #2:

The firm was asked to submit dissolution testing data for the test and reference products using _____

_____ and the _____) with an optimum rotation speed (not to exceed _____). The sampling times should be at 20, 40, 60, 90, and 120 minutes.

RESPONSE #2:

The firm submitted dissolution testing data in various media summarized in Table 1. Percent of Isotretinoin dissolved in 120 minutes was very low in each medium, except in _____. Based on results of this study, the firm proposes the following method:

Medium: _____
 Volume: _____
 Apparatus: _____
 RPM: _____
 Assay Method: _____

The data are summarized in Table 2.

COMMENT:

Currently there is no FDA or USP method listed for the dissolution testing of Isotretinoin Soft Gelatin Capsules.

III. DEFICIENCIES OF THE CURRENT SUBMISSION:

1. The Division of Bioequivalence recommends dissolution testings be conducted for the test and reference products, 10, 20, and 40 mg using the following conditions:

- Buffer solutions (pH in range of _____ containing _____)
- The _____, with a rotation speed of _____ and _____ rpm.
- Sampling time: at 120 minutes for preliminary studies.
- Sampling times: at 20, 40, 60, 90, and 120 minutes for the proposed method. Specifications should be proposed.

2. Degradation of isotretinoin to tretinoin should be tested for the dissolution samples. The results should be submitted to the Division of Bioequivalence.

3. The lots used for the dissolution testing of the reference products, 20 mg (lot U3591) and 40 mg (lot U0580) are not the same as those that were used in the bioequivalence studies. However, lot U0538 that was used in the bioequivalence study for 40 mg strength, expired on 8/2001. But the lot U3584 that was used in the bioequivalence study for 20 mg Capsules has not been expired (expiration date: 9/2002). Therefore, the firm should explain the reason that the unexpired lot (U3584) for 20 mg reference product was not used for the dissolution testing.

IV. RECOMMENDATIONS:

1. The single dose, fasting bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, 20 mg (batch #1077708) comparing it to Accutane^R Capsules, 20 mg (lot #U3584) by Roche Laboratories is found acceptable by the Division of Bioequivalence.

2. The dissolution testing submitted by Ranbaxy Laboratories Limited on its 10, 20, and 40 mg Isotretinoin Capsules comparing them with 10, 20, and 40 mg Accutane^R Capsules by Roche Laboratories is found incomplete by the Division of Bioequivalence.

3. The waiver of bioequivalence study requirements for Isotretinoin Soft Gelatin Capsules, 10 mg is not granted.

4. The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, 12/18/2001
 Farahnaz Nouravarsani, Ph.D.
 Review Branch III
 Division of Bioequivalence

RD INITIALED B. Davit

FT INITIALED B. Davit

BMD 12/18/01

Barbara M Davit

Date 12/18/01

Concur:

Dale P. Conner
 Dale P. Conner, Pharm.D.

Date 12/18/01

Director

Division of Bioequivalence

F. Nouravarsani/Draft: 12-18-2001/76041STA.D01

*dissolution
method*

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information

TABLE 2:

DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI)

Method: Proposed by the firm
Analyte: _____
Dosage Form and Strengths: Soft Gelatin Capsules
 10 mg, 20 mg, and 40 mg
No. of Units Tested: 12 Capsules
Medium: _____
Volume: _____
Apparatus: _____
RPM: _____
Assay Method: _____
Proposed Specifications: ---

Results:

%Dissolved

Time, Minutes	Test Product			Reference Product		
	Mean%	Range%	CV%	Mean%	Range%	CV%
	10 mg Lot #: 1077712 Exp. Date: 5/02			10 mg Lot No.: U2590 Exp. Date: 10/02		
20	22	_____	16.8	24	_____	14.2
40	42	_____	16.7	41	_____	8.5
60	62	_____	2.7	60	_____	8.8
90	76	_____	5.4	73	_____	7.1
120	93	_____	3.1	85	_____	6.9

%Dissolved

Time, Minutes	Test Product			Reference Product		
	Mean%	Range%	CV%	Mean%	Range%	CV%
	20 mg Lot #: 1077708 Exp. Date: 5/02			20 mg Lot No.: U3591 Exp. Date: 11/02		
20	31	_____	8.4	29	_____	9.3
40	50	_____	7.8	47	_____	10.0
60	60	_____	4.8	58	_____	6.4
90	79	_____	5.8	77	_____	5.2
120	91	_____	4.3	85	_____	4.6

%DissolvedTime,
MinutesTest Product
40 mg
Batch #: 1077652
Exp. Date: 5/02Reference Product
40 mg
Lot No.: U0580
Exp. Date: 08/02

	<u>Mean%</u>	<u>Range%</u>	<u>CV%</u>		<u>Mean%</u>	<u>Range%</u>	<u>CV%</u>
20	32	 	22.2		31	 	7.7
40	46	 	14.1		47	 	10.9
60	61	 	9.8		58	 	8.6
90	80	 	7.1		78	 	5.0
120	92	 	3.8		86	 	4.4

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-041

APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCTS:

Isotretinoin Capsules USP
10 mg, 20 mg, and 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The Division of Bioequivalence recommends dissolution testings be conducted for the test and reference products, 10, 20, and 40 mg using the following conditions:

- Buffer solutions (pH in range of _____ containing _____
- _____ with a rotation speed of _____ and _____ rpm.
- Sampling time: at 120 minutes for preliminary studies.
- Sampling times: at 20, 40, 60, 90, and 120 minutes for the proposed method. Specifications should be proposed.

2. Please test degradation of isotretinoin to tretinoin for the dissolution samples. The results should be submitted to the Division of Bioequivalence.

3. The lots used for the dissolution testing of the reference products, 20 mg (lot U3591) and 40 mg (lot U0580) are not the same as those that were used in the bioequivalence studies. However, lot U0538 that was used in the bioequivalence study for 40 mg strength, expired on 8/2001. But the lot U3584 that was used in the bioequivalence study for 20 mg Capsules has not been expired (expiration date: 9/2002). Please explain the

**APPEARS THIS WAY
ON ORIGINAL**

reason that the unexpired lot (U3584) for 20 mg reference product was not used for the dissolution testing.

Sincerely yours,



Dale P. Conner, Pharm.D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-041
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HFD-658/F. Nouravarsani

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Printed in final on 12/18/2001

Endorsements: (Final with Dates)

HFD-658/F. Nouravarsani, *Farahnaz Nouravarsani, 12/18/2001*

HFD-658/B. Davit *BD 12/18/01*

HFD-650/D. Conner *DC 12/18/01*

BIOEQUIVALENCY - DEFICIENCY

SUBMISSION DATE:

12/04/2001

ok **STUDY AMENDMENT (STA)**

Strengths: All

OUTCOME: IC

OUTCOME DECISION: IC

WINBIO COMMENTS: INCOMPLETE.

**APPEARS THIS WAY
ON ORIGINAL**

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 76-041 **SPONSOR:** Ranbaxy Laboratories Limited
DRUG AND DOSAGE FORM: Isotretinoin Capsules USP
STRENGTHS: 10 mg, 20 mg, and 40 mg
TYPE OF STUDIES: Fasting and Non-Fasting (Single-Dose)
CLINICAL STUDY SITE: _____
ANALYTICAL SITE: _____

STUDIES SUMMARY:

All studies, fasting and fed for the 40 mg product, and fasting for the 20 mg product are found Acceptable.

DISSOLUTION TESTING:

Acceptable.

WAIVER:

Waiver is granted for the 10 mg product.

DSI INSPECTION STATUS

Inspection needed: <u>No.</u>	Inspection status:	Inspection results:
First Generic: <u>No.</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Farahnaz Nouravarsani, Ph.D. **BRANCH:** 3
INITIAL: Farahnaz Nouravarsani **DATE:** 4/15/02

ACTING TEAM LEADER: Moheb Makary, Ph.D. **BRANCH:** 3
INITIAL: MM **DATE:** 4/15/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner,
Pharm.D.
INITIAL: DP **DATE:** 4/30/02

5.12

Isotretinoin Capsules USP
 10 mg, 20 mg, and 40 mg
 ANDA 76-041
 Reviewer: F. Nouravarsani
 76041A0202.doc

Ranbaxy Laboratories Limited
 Gurgaon, India
 Submission Dates:
 02/04/2002
 04/01/2002

REVIEW OF TWO AMENDMENTS

I. CONTENTS OF THE CURRENT SUBMISSIONS:

Responses to the deficiencies of the submissions dated 12/04/01 and 02/04/02.

II. DEFICIENCIES AND RESPONSES:

DEFICIENCY #1:

The Division of Bioequivalence recommended dissolution testings be conducted for the test and reference products, 10, 20, and 40 mg using the following conditions:

- Buffer solutions (pH in range of _____, containing _____)
- The _____, with a rotation speed of _____ and _____ rpm.
- Sampling time: at 120 minutes for preliminary studies.
- Sampling times: at 20, 40, 60, 90, and 120 minutes for the proposed method. Specifications should be proposed.

RESPONSE #1:

The preliminary dissolution tests were performed on the highest strength of the test and reference products (Table 1). Based on results of the preliminary studies conducted at 120-minute sampling time, the firm proposed the following method (method A) and specifications:

Method A:

Medium: _____

Volume: _____

Apparatus: _____

RPM: _____

Proposed Specifications:

NLT _____ (Q) of isotretinoin is dissolved in 120 minutes.

The F2 values using the dissolution testing data from the **test and reference products** are summarized as follows:

Strength	F2 Value		
	Method A	Method B	Method C
10 mg	55.2	75.7	76.4
20 mg	57.5	70.0	75.0
40 mg	52.6	59.9	60.2

COMMENTS:

1. Currently there is no FDA or USP method listed for the dissolution testing of Isotretinoin Soft Gelatin Capsules.
2. The dissolution testing data are found acceptable for the method A, B, or C. However, the Division of Bioequivalence recommends the method B (Table 3) with the specifications of "NLT ~~—~~ (Q) of isotretinoin is dissolved in 90 minutes".

The method B is recommended because the rotation speed of the apparatus is lower for this method compared with the method A, and the concentration of the surfactant is lower compared with the methods A and C.

3. The F2 values are all above 50.

DEFICIENCY #2:

The firm was asked to test degradation of isotretinoin to tretinoin for the dissolution samples.

RESPONSE #2:

Degradation of isotretinoin to tretinoin in the dissolution samples was tested for preliminary studies as well as the final comparative dissolution studies. The tretinoin levels were in a range of ~~—~~ for the dissolution samples at 120-minute sampling time for both the test and reference products (Tables 1 and 2).

DEFICIENCY #3:

The lots used for the dissolution testing of the **reference products**, 20 mg (lot U3591) and 40 mg (lot U0580) were not the same as those that were used in the bioequivalence studies. However, lot U0538 that was used in the bioequivalence study for 40 mg strength, expired on 8/2001. But the lot U3584 that was used in the bioequivalence study for 20 mg Capsules had not been expired (expiration date: 9/2002). **The firm was asked to explain the reason that the unexpired lot (U3584) for 20 mg reference product was not used for the dissolution testing.**

RESPONSE #3:

The firm responded that when Ranbaxy obtained the 20 mg reference product, the lot #U3584 was not available and only lot #U3591 could be obtained.

Furthermore, for the recently conducted dissolution testing, the firm could not obtain lot #U3584 or U3591 for the reference product, 20 mg.

III. DEFICIENCY OF THE CURRENT SUBMISSION: None.

IV. RECOMMENDATIONS:

1. The single dose, **fasting** bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, **40 mg** (batch #1077652) comparing it to Accutane^R Capsules, 40 mg (lot #U0538) by Roche Laboratories is found acceptable by the Division of Bioequivalence.
2. The single dose, **non-fasting** bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, **40 mg** (batch #1077652) comparing it to Accutane^R Capsules, 40 mg (lot #U0538) by Roche Laboratories is found acceptable by the Division of Bioequivalence.
3. The single dose, **fasting** bioequivalence study submitted by Ranbaxy Laboratories Limited on its Isotretinoin Capsules, **20 mg** (batch #1077708) comparing it to Accutane^R Capsules, 20 mg (lot #U3584) by Roche Laboratories is found acceptable by the Division of Bioequivalence.
4. The **dissolution** testing submitted by Ranbaxy

Laboratories Limited on its 10 mg (lot #1077712), 20 mg (lot #1077708), and 40 mg (lot #1077652) Isotretinoin Capsules comparing them with 10 mg (lot #U2590), 20 mg (lot #U3590), and 40 mg (lot #U0588) Accutane^R Capsules by Roche Laboratories is found acceptable by the Division of Bioequivalence.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in _____

_____ The test products should meet the following specifications:

Not less than $\frac{1}{2}$ (Q) of the labeled amount of the drug in the dosage form is dissolved in 90 minutes (interim).

6. The **waiver** of bioequivalence study requirements for Isotretinoin Soft Gelatin Capsules, **10 mg** is granted based on 21 CFR 320.22 (d) (2).

Farahnaz Nouravarsani, 4/15/02

Farahnaz Nouravarsani, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED M. Makary

FT INITIALED M. Makary *Mohab H. Makary* Date *4/15/02*

Concur:

Dale P. Conner

Date *4/30/02*

Dale P. Conner, Pharm.D.

Director

Division of Bioequivalence

F. Nouravarsani/Draft: 04-15-2002/76041A0202.doc

*dissolution
methods*

Redacted _____ 7

Page(s) of trade

secret and /or

confidential

commercial

information

CC: ANDA 76-041
DIVISION FILE
HFD-658/F. Nouravarsani

Endorsements: (Final with Dates)

HFD-658/ F. Nouravarsani, *Farahnaz Nouravarsani, 4/15/02*

HFD-658/ M. Makary *MHM @ silo 2*

HFD-650/ D. Conner *DK 4/30/02*

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Printed in final on 4/15/02

BIOEQUIVALENCY - ACCEPTABLE **SUBMISSION DATES: 02/04/2002**
04/01/2002

STUDY AMENDMENT (A) **Strengths: All**
(02/04/2002) **Outcome: AC**

STUDY AMENDMENT (A) **Strengths: All**
(04/01/2002) **Outcome: AC**

OUTCOME DECISION: AC - Acceptable

WINBIO COMMENT: AC

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-041

**ADMINISTRATIVE
DOCUMENTS**

Ho, Sarah

From: Adams, Shawnte L
Sent: Thursday, May 23, 2002 12:59 PM
To: Ho, Sarah
Subject: RE: ANDA 76-041

The Ranbaxy site in _____ does not perform the function of drug substance manufacturer (as stated in the comments in the milestone for OC Recommendation) which is why it was withheld; however the other Ranbaxy site in Punjab, India is an acceptable drug substance manufacturer. Therefore we made an acceptable recommendation based on the fact that there was an acceptable drug substance manufacturer for this product.

Thank you,
Shawnte Adams
Project Specialist, HFD-322
Division of Manufacturing & Product Quality
301-827-7276
301-594-1033 fax

-----Original Message-----

From: Ho, Sarah
Sent: Wednesday, May 22, 2002 3:05 PM
To: CDER EESQUESTIONS
Cc: Sood, Ramesh
Subject: ANDA 76-041

Good afternoon.

Could you please provide some clarification?

When we bring up this application in EES, Ranbaxy Laboratories of ' _____ , is listed as "WITHHOLD" (given 05-OCT-2001); however, the overall recommendation is "Acceptable" (given 18-DEC-2001). Thank you in advance.
Sarah

APPEARS THIS WAY
ON ORIGINAL

Golson, Lillie D

From: Golson, Lillie D
Sent: Tuesday, May 07, 2002 11:17 AM
To: Abha Pant (E-mail)
Subject: ANDA 76-041

Importance: High

To Holders of Approved Abbreviated New Drug Applications (ANDAs) for Isotretinoin Capsules:

Below are recommendations from the Office of Drug Safety for the Isotretinoin Prescription Compliance Survey. We ask that you review these and submit your proposed plan for conducting the survey. This component must be found acceptable prior to approving your application.

Additionally, it has come to our attention that isotretinoin is being used in veterinary medicine and veterinarians will be participating in Accutane's SMART program. To differentiate prescriptions written for humans from those written for dogs, we ask that you propose a distinctive way to differentiate the stickers. This should be done ASAP but is not a condition of approval.

Finally, electronic prescribing is very much on the radar screen. This is especially true for prescribers working for the Department of Defense and the Veterans Administration. Please propose a mechanism to ensure compliance with the terms of the risk management program using electronic prescribing. Again, this should be done ASAP but is not a condition of approval.

As always, contact me if you have questions.

Thank you.

Recommendations for Generic Drug Manufacturers

It is recommended that generic drug manufacturers contemplating marketing of isotretinoin conduct a prescription compliance survey designed to measure compliance with use of qualification stickers. FDA's primary concern is the assessment of compliance with stickered prescriptions for isotretinoin as a molecule. Essential elements of this survey are described below:

- **Methods:** The survey protocol should provide a detailed description of the population to be surveyed and the sampling process, including an assessment of the representativeness of the pharmacies surveyed compared with all US retail pharmacies. Pharmacy characteristics that are anticipated to affect compliance with the use of qualification stickers, and which should be critically evaluated in terms of representativeness include store type, geographical region, population density served, and total prescription volume. The survey protocol should describe methods (such as incentives and follow-up phone calls) to achieve a survey response rate of at least 60%.
- **Survey Endpoints:** The primary objective of the survey should be to measure compliance with use of the qualification stickers. Therefore, the primary survey endpoint should be the total number of stickered isotretinoin (any brand) prescriptions divided by the total number of isotretinoin (any brand) prescriptions filled. The secondary objective should be to measure the completeness of the stickers used. A correctly completed qualification sticker should provide the patient's gender and the qualification date, if the patient is female. Hence, the secondary survey

endpoint should be the total number of correctly completed isotretinoin (any brand) stickered prescriptions divided by the total number of isotretinoin (any brand) stickered prescriptions filled.

Data Collection: Data should be collected retrospectively to prevent pharmacists from modifying their behaviors toward dispensing isotretinoin. That is, pharmacists should be responding about isotretinoin prescriptions written in a time period prior to their initial recruitment in the survey. Pharmacies that refuse to participate in the survey should be removed from the sampling frame and not be recontacted. A description of the plan to assure that data are not collected from pharmacies that have already participated, or have refused to participate in any Accutane or isotretinoin survey should be provided. Data elements collected in the survey should include:

- presence of a qualification sticker
 - if a qualification sticker was used, whether or not the qualification date blank was appropriately completed
 - product name on the prescription, manufacturer, strength, number of authorized refills, mode of receipt (original in person, phoned, faxed, emailed)
 - whether or not a Medication Guide was dispensed with the drug
 - patient characteristics, including gender, and age
 - pharmacy characteristics, including geographic region, urban vs. rural location, and pharmacy type (independent, grocery, small chain, large chain)
 - an estimate of the number of isotretinoin prescriptions presented but not filled by the pharmacy during the time period under study
- **Analysis Plan:** Based upon the anticipated response rate and other factors, the estimated number of pharmacies and prescriptions that will be surveyed should be provided along with power estimates or confidence intervals for these numbers. A detailed description of statistical analyses that will be performed on the primary and secondary study endpoints should be provided.
 - **Data Validation:** A validation step is essential to ensure the completeness and accuracy of the self-reported data collected in the survey. A proposal to validate some portion of the data collected should be included in the survey protocol. The proposal should provide for validation of a random sample of at least 15% of survey responses, and take into consideration each pharmacy stratum, as characterized by store type, geographical region, population density served, and total prescription volume.

Assessment Metrics: The adequacy of the generic drug manufacturer's risk management program for isotretinoin will be a FDA review issue for re-evaluation on a continuing basis. The manufacturer should propose benchmarks against which compliance with stickered prescriptions can be measured. For example, the proposal could state what percent of prescriptions filled by pharmacists will be expected to have isotretinoin stickers at the end of the first year of implementation of the risk management program, and what percent by the end of the second year. In addition, the proposal could state what percent of prescriptions filled by pharmacists should have correctly completed stickers at one and two years post-implementation.

Expectation: We recommend that at least one survey wave be conducted, fully analyzed, and submitted to FDA for review on or before June 30, 2003.

Non-retail sales: Generic drug manufacturers should track sales volume of their product through non-retail pharmacies (e.g., mail order, internet sales by valid US pharmacies, closed staff HMOs) on a periodic basis and submit this information to FDA on a quarterly basis.

Tracking:

Recipient
Abha Pant (E-mail)
Golson, Lillie D

Delivery
Delivered: 5/7/02 11:17 AM

Golson, Lillie D

From: System Administrator [postmaster@ranbaxy.com]
Sent: Tuesday, May 07, 2002 11:20 AM
To: GOLSONL@cder.fda.gov
Subject: Delivered: ANDA 76-041

Importance: High



ANDA 76-041

<<ANDA 76-041>> Your message

To: Abha Pant (E-mail)
Subject: ANDA 76-041
Sent: Tue, 7 May 2002 11:16:53 -0400

was delivered to the following recipient(s):

Abha Pant on Tue, 7 May 2002 12:20:13 -0400
MSEXCH:MSExchangeMTA:RPI:PRI_MSG_01

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

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

DATE: July 26, 2002

FROM: Denise Cook, M.D., HFD-540
Medical Officer
Division of Dermatologic and Dental Drug Products

THROUGH: Jonathan Wilkin, M.D., HFD-540
Director
Division of Dermatologic and Dental Drug Products

SUBJECT: Package Insert Labeling for Approval of Isotretinoin Capsules,
10 mg, 20 mg, and 40 mg

TO: Director, Office of Generic Drugs

DC 7/30/02 I agree but with the following exception (see comment attached).

JW 7/30/02 - See Attached Comments

The Office of Generic Drugs (OGD) consulted this division regarding acceptable package insert labeling for generic Accutane (isotretinoin) capsules. OGD has asked if the generic firms could carve out information from pediatric studies, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses. This labeling, which was approved on May 2, 2002, was granted 3 years of Hatch-Waxman exclusivity. A meeting was held to address this issue on June 26, 2002.

The meeting included representatives from The Office of Chief Counsel, Office of Generic Drugs, Office of Pediatric Drug Development and Program Initiatives, and Dr. Denise Cook of the Division of Dermatologic and Dental Drug Products. The approved pediatric protected additions to the Accutane labeling, and the proposed generic carve-outs were discussed. The meeting participants reviewed each section of the current Accutane package insert and commented on the impact of each proposed deletion on the safety and effectiveness of the drug product. The conclusion reached was that generic firms could carve-out the pediatric labeling sections without rendering generic products less safe or effective for all remaining non-protected conditions of use.

Under the approach proposed by OGD and found acceptable to this division, the following table summarizes the changes.

The Division of Dermatologic and Dental Drug Products believes that generic Accutane (isotretinoin) capsules applications can be approved without including the pediatric use sections in the labeling. Omitting the protected text, as indicated above, will not render the generic products less safe or effective than the listed drug for all remaining non-protected conditions of use.

Sections changed:	Proposed ANDA Change:	Accutane Labeling:	Description of Change in ANDA:
<p>CLINICAL PHARMACOLOGY (Special Patient Populations)</p>	<p><i>Special Patient Populations: Pediatric Patients:</i> 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, <u>this drug product is not labeled for pediatric use.</u></p>	<p><i>Special Patient Populations: Pediatric Patients:</i> The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients 18 years) who received Accutane for the treatment of severe recalcitrant nodular acne. In both age groups, 4-oxo-isotretinoin was the major metabolite; tretinoin and 4-oxo-tretinoin were also observed. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in Table 3 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.</p> <p>Table 3. Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12 to 15 Years of Age Mean ...</p> <p>In pediatric patients (12 to 15 years), the mean +/- SD elimination...</p>	<p>Entire sub-section carved out and pediatric disclaimer used.</p>
<p>PRECAUTIONS (Pediatric Use)</p>	<p><i>Pediatric Use:</i> 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: <i>General</i>).</p> <p>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</p>	<p><i>Pediatric Use:</i> The use of Accutane in pediatric patients less than 12 years of age has not been studied. The use of Accutane for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see PRECAUTIONS: <i>General</i>). Use of Accutane in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (18 years). Results from this study demonstrated that Accutane, at a</p>	<p>Revised the first paragraph.</p>

marketing exclusivity rights, this drug product is not labeled for pediatric use.

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

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

dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

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

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

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Attachment to Memorandum from Office of Generic Drugs concerning
Package Insert Labeling for Approval of Isotretinoin Capsules

Date: July 3, 2002

To: Director, Office of Generic Drugs

From: Denise Cook, M.D., HFD-540 *DC 7/30/02*
Medical Officer
Division of Dermatologic and Dental Drug Products

THROUGH: Jonathan Wilkin, M.D., HFD-540 *JW 7/30/02*
Division Director
Division of Dermatologic and Dental Drug Products

SUBJECT: Package Insert for Labeling for Approval of
Isotretinoin Capsules, 10 mg, 20 mg, and 40 mg

The approved letter for NDA 18-662/S-043, dated May 2, 2002, explicitly states, "This supplemental new drug application does not significantly affect the size of the patient population to be given the drug, since Accutane was already approved for the treatment of severe recalcitrant nodular acne without reference to age restrictions." It is not understood how exclusivity based on S-043 would remove a population implied in the indication before S-043 was submitted. We have no difficulty with the carve-outs, but we believe that the ANDA change, "... this drug product is not labeled for pediatric use" (which appears twice) would remove the principal population from pre-S-043 labeling and would be more than Hoffmann La-Roche added with S-043.

**APPEARS THIS WAY
ON ORIGINAL**

APPROVAL PACKAGE SUMMARY FOR 76-041

ANDA: 76-041

FIRM: Ranbaxy Pharmaceuticals Inc.

DRUG: Isotretinoin

DOSAGE: Capsules

STRENGTH: 10 mg, 20 mg, 40 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 12/18/01 *12/20/02 e.m.m.*

BIO STUDY/BIOEQUIVALENCE: Bio is satisfactory 4/30/02

METHOD VALIDATION: The drug substance and the drug product are compendial.

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at $40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$ and 24 months room temperature stability data at $25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$ for product packaged in blisters for all strengths.

LABELING REVIEW STATUS: Acceptable 12/18/02

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the batch records for the proposed batch sizes for production runs are the same as those for the ANDA exhibit batches. Also copies of the executed batches for 10 mg batch #1077712 (_____ capsules), 20 mg batch #1077708 _____ capsules, and 40 mg batch #1077652 _____ capsules) are provided. The firm will be using the same drug substance manufacturer, same process, and same equipment.

COMMENTS: The application is approvable.

N. Nashed
Reviewer: Nashed E. Nashed, Ph.D.

12/19/02
Date: 8/1/02

Supervisor: James M. Fan

Date: 8/9/02

J. M. Fan *12/20/02*

Ho, Sarah

From: Dillahunt, Michelle
Sent: Thursday, December 19, 2002 3:02 PM
To: Ho, Sarah
Subject: FW: ANDA 76-041 Sotret (isotretinoin)

-----Original Message-----

From: Toyer, Denise P
Sent: Thursday, December 19, 2002 2:54 PM
To: Golson, Lillie D
Cc: Greenberg, Harry; Dillahunt, Michelle; Beam, Sammie; Holquist, Carol A
Subject: ANDA 76-041 Sotret (isotretinoin)

Lillie,

In our conversation yesterday, you noted that the 90 day DMETS' acceptance for the proposed name, Sotret, for this ANDA expired on December 13, 2002. OGD is prepared to take an action on this application this week. As we discussed the usual procedure is to resubmit this name for another final review. However, due to the time constraints, I agreed to see if we could expedite this review, so that we would not delay your approval. We note that you have already discussed any proprietary name issues pertaining to this isotretinoin product with the OND review division. Therefore, DMETS has no objections to the use of the proposed proprietary name 'Sotret' for ANDA 76-041 (ODS consult # 01-0111-3).

Please let me know if we can be of further assistance.

Thanks.
Denise

Denise Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
301-827-7609

APPEARS THIS WAY
ON ORIGINAL

76041
1.1

Clinical Consult
Essential Components for Isotretinoin Risk Management Plans

HFD# 017593

Date of Consult: March 7, 2001
Date Received: March 27, 2001
Response Date: March 30, 2001

To: Lillie Golson
Office of Generic Drugs

From: Kathryn O'Connell, M.D. Ph.D. *KOC 4/4/01*
Medical Officer, HFD-540

Through: Jonathan Wilkin, M.D. *Jon Wilkin 4/4/01*
Division Director, HFD-540

Background: The risk management program for Accutane (isotretinoin) is currently evolving from a voluntary to a mandatory program linking dispensing to negative pregnancy tests for female patients. In response to your question about the essential elements of each component of the risk management program, we are referring not to this planned program, but to the Accutane Pregnancy Prevention Program referred to in the May 2000 revised Accutane labeling.

The elements commented on below are not detailed templates for appropriate tools. Instead, the recommendations identify general features we consider necessary based on the risk management *goals* of each component. Once sponsors submit their design for meeting each of these goals, we are available to advise you about adequacy of the details they propose. We are commenting here only on physical tools (such as written material, kits, surveys etc). For other aspects of the risk management program, we recommend that the advice and wording in the Accutane labeling be preserved in its entirety.

Please note that the formatting of the labeling copy below may not be exactly preserved from the PDF file original. This copy is intended only as a reference point for the component (highlighted in red) upon which we are commenting.

- Please be advised that a more rigorous plan is under development to prevent fetal exposure to Accutane. This plan will include mandatory prescriber education/registration. It will also include mandatory negative pregnancy tests prior to dispensing of 30 day supply. This will entail a "registry" for patients whereby data needed to authorize dispensing are entered into a database for accession by dispensing pharmacists. In addition, the new program may employ an "opt-out" feature for the more detailed patient Survey, such that voluntary participation is "default". Once this type of plan is implemented for any version of isotretinoin, plans for all isotretinoin products on the market must simultaneously address these important public health safety goals with the same degree of rigor.
- We strongly recommend that generic sponsors NOT assign proprietary names to their isotretinoin versions. The reason is that Accutane safety is no doubt greatly enhanced by 20 years of name recognition linking it to birth defects. The FDA, birth defect prevention organizations, and all generic isotretinoin manufacturers will need to embark on a public health education campaign to establish such linkage for "isotretinoin". This campaign should include consumers and all health care professionals, not just prescribers.
- We recommend consulting OPDRA for their advice on the question you posed to us. Please feel free to forward this consult response to them for reference.

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 05/30/01

DUE DATE: 08/24/01

OPDRA CONSULT #: 01-0111

TO: Peter Rickman
Acting Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-611

THROUGH: Harvey Greenberg
Project Manager
HFD-615

PRODUCT NAME:
_____ (isotretinoin capsules, USP)
10 mg, 20 mg, 40 mg

MANUFACTURER: Ranbaxy Laboratories, Ltd.

ANDA # 76-041

SAFETY EVALUATOR: Marci Lee, Pharm.D.

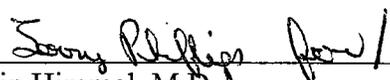
SUMMARY: In response to a consult from the Office of Generic Drugs, Division of Labeling and Program Support, OPDRA conducted a review of the proposed proprietary name, _____, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, _____. OPDRA has no objection to the use of a proprietary name for this product. OPDRA recommends revising the labels and labeling as outlined in section III of this review. OPDRA recommends that all manufacturers of isotretinoin promote its safe use with the same practices as the innovator, outlined in section II-C of this review.

**APPEARS THIS WAY
ON ORIGINAL**



Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

 8/22/01

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 6, 2001

ANDA NUMBER: 76-041

NAME OF DRUG: _____ (isotretinoin capsules, USP) 10 mg, 20 mg, 40 mg

ANDA HOLDER: Ranbaxy Laboratories, Ltd.

I. INTRODUCTION

This consult was written in response to a request from the Office of Generic Drugs, Division of Labeling and Program Support for assessment of the proposed proprietary drug name, _____ regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

_____ (isotretinoin) is a retinoid, which is indicated for the treatment of nodular acne. Isotretinoin inhibits sebaceous gland function and keratinization. The recommended dosage for _____ is 0.5 to 2 mg/kg given in two divided doses daily for 15 to 20 weeks. Isotane will be available as 10mg, 20 mg and 40 mg soft gelatin capsules.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was conducted^v. The Saegis^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies to simulate the prescription ordering process.

ⁱ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

^{iv} The Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, —. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Nine proprietary names were identified in the Expert Panel Discussion that were thought to have potential for confusion with —. These products are listed in the table, along with the dosage forms available and usual FDA-approved dosage.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	10 mg, 20 mg, 40 mg capsules	10 mg po BID	
Isordil Titrados Also: Isordil Tembids	isosorbide dinitrate 5 mg, 10 mg, 20 mg, 30 mg, 40 mg tablets; 40 mg SR capsules 40 mg SR tablets	Initial dose is 5 to 20 mg; maintenance dose is 10 to 40 mg every 6 hours. <i>Sustained release:</i> The initial dose is 40 mg; maintenance controlled release dose is 40 to 80 mg every 8 to 12 hours.	L/A
Soriatane	acitretin; 10 mg, 25 mg capsules	Doses of 25 or 50 mg are given with food once daily	S/A
Loxitane	loxapine 5 mg, 10 mg, 25 mg, 50 mg capsules; 25 mg/mL in 120 mL (with dropper) oral concentrate; 50 mg/mL in 10 mL vials IM injection	10 mg by mouth twice daily Usual range is 60 to 100 mg/day. Administer IM (not IV) in 12.5 to 50 mg doses at intervals of 4 to 6 hours or longer, many patients respond to twice-daily dosing.	S/A
Artane	trihexyphenidyl 2 mg and 5 mg tablets; 5 mg SR capsules and 2 mg/5mL elixir	Initially, 1 to 2 mg the first day; increase by 2 mg increments at intervals of 3 to 5 days, until a total of 6 to 10 mg is given daily; best if divided into 3 doses and taken at mealtimes.	L/A
Accutane	isotretinoin 10 mg, 20 mg, 40 mg capsules	Initial dose is 0.5 to 1 mg/kg/day (range, 0.5 to 2 mg/kg/day) divided into 2 doses for 15 to 20 weeks. Administer isotretinoin with food.	S/A
Mitotane (established name)	mitotane 500 mg tablets	Start at 2 to 6 g/day in divided doses, 3 or 4 times daily	S/A
Isoptin Also: Isoptin SR 120 mg, 180 mg, 240 mg SR tablets	verapamil 40 mg, 80 mg, 120 mg tablets injection: 2.5mg/mL (2 mL, 4 mL)	Usual initial dose is 80 to 120 mg 3 times a day. <i>Sustained release:</i> Usual daily dose is 240 mg/day in the morning.	S/A
“isophane” insulin (NPH) (established name)	“isophane” insulin (NPH) 100 units/mL. Prefilled syringes, cartridges and vials. (Available as part of the combination for 70/30 insulins.)	Individualized dosing	S/A

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
	10 mg, 20 mg, 40 mg capsules	10 mg po BID	
Isocaine HCl	mepivacaine 3% injection 2% with 1:20,000 levonordefrin	Procedure dependent dosing; anesthesia agent	S/A

* Frequently used, not all inclusive

** L/A = look-alike and S/A = sound-alike

2. DDMAC did not object to the use of the name,

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

Three separate studies were conducted within FDA to determine the degree of confusion of with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescription for . These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<i>Outpatient:</i> <u> </u> 10 mg Sig: 1 po bid #60 No refill	<i>Outpatient:</i> <u> </u> 10 mg two times daily. Dispense 60 tablets; No refill
<i>Inpatient:</i> <u> </u> 10 mg bid	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	<u> </u> response	Other response
Written: Inpatient	30	16 (53 %)	4 (25 %)	12 (75 %)
Written Outpatient	28	19 (68 %)	8 (42 %)	11 (58 %)
Verbal: Outpatient	27	17 (63 %)	0 (0 %)	17 (100%)
Total:	85	52 (61 %)	12 (23 %)	40 (77%)

Although HFD-540 sent a clinical consult to OGD strongly recommending that generic isotretinoin NOT be assigned a proprietary name, the sponsor has the legal right to a proprietary name. Although it is OPDRA and CDER's current policy to NOT allow the use of a different proprietary name for the SAME active ingredient by the SAME manufacturer, this policy does not apply where there is a different manufacturer.

In response to the HFD-540 concern that another proprietary name may take away from the Accutane safety campaign by Roche Pharmaceuticals, OPDRA recognizes a safety strategy that is more than a propriety name alone. This has been true of other agency approvals (e.g. generic approvals of Clozaril).

Currently, the safe use of isotretinoin is promoted by the strong warnings on labels/labeling and the innovator's Pregnancy Prevention Program (PPP). The PPP materials include a contraceptive booklet, checklists to help assess whether patients could adhere to the drug's requirements, and consent forms that patients sign to acknowledge their understanding of the risk of birth defects. The innovator also set up a toll-free line, made contraceptive information available in 13 languages and offered to pay for contraceptive counseling and pregnancy testing by a specialist.

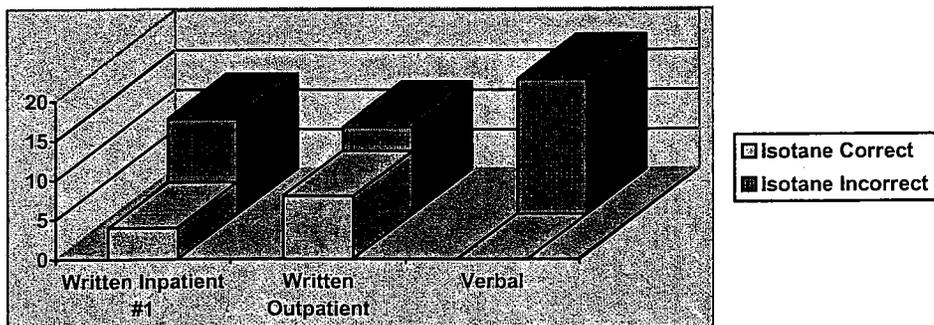
[^]Meadows M. The power of accutane. *FDA Consumer* 18-23, March-April 2001.

In reviewing the proprietary name, _____, the primary concerns raised by the expert panel were related to several sound-alike and look-alike names that already exist in the US marketplace. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Isotane could be confused with Isocaine, Loxitane, Artane, Accutane, Soriatane, Mitotane, Isordil, or Isoptin. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names, except for *Isophane*, which is used to describe a type of insulin preparation. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, Isotane.

Isordil and ' _____ may look similar because they share the common ' _____ and have the same number of letters. Although there is no overlapping indication, all of the dosage strengths for _____ overlap with *Isordil*. Additionally there is a sustained release formulation of *Isordil* (*Isordil Tembids*), which are administered twice daily similar to _____ If a patient received *Isordil* in error, they may experience the cardiovascular effects associated with *Isordil*.

Isordil

Soriatane was identified by the expert panel to have potential for sound-alike confusion with _____ Similar to _____ *Soriatane* is a retinoic acid analog and carries a strong pregnancy warning. There is overlap in the dosage strength of 10 mg capsules. Although *Soriatane* has a different indication, both agents are used to treat conditions of the skin and may be prescribed by the same specialists in a similar context of use. These factors increase the likelihood for confusion between *Soriatane* and _____



Among the two written prescription studies, 23 of 35 (66 %) participants interpreted the name incorrectly. Seven respondents misinterpreted the proposed name, _____, as *Isofane*. Other incorrect responses were *Ifotane*, *Ipofane*, *Isophane*, *Fiotine*, *Flotene*, *Fortane*, *Ilotene*, *Irotene*, *Isotene*, *Isotine*, *Itotine*, and *Trotine*. None of the incorrect responses were of marketed products. However, *Isophane* is a type of insulin (NPH), which can be used alone or in combination to make the 70/30 insulin products.

Among the verbal prescription study participants for _____, 17 of 17 (100 %) participants interpreted the name incorrectly. However, all of the incorrect name interpretations were phonetic variations of "_____" and none of the incorrect responses were marketed products. Most participants interpreted the name as *Isoten*. Other incorrect responses were *Isophane*, *Isotan*, *Isotin*, and *Isoton*. Again, *Isophane* is a type of insulin (NPH), which can be used alone or in combination to make the 70/30 insulin products.

C. SAFETY EVALUATOR RISK ASSESSMENT

In general, any product that could be confused with _____ carries an additional risk because of the pregnancy category X rating for _____. Although there is a recommended special distribution process for the prescribing and dispensing of _____, it is voluntary. The recommendation is for a patient to receive two pregnancy tests, prior to receiving this medication, to demonstrate that she is not pregnant. In addition, there is a patient consent form, which further emphasizes the risks associated with _____ and the recommendations for preventing pregnancy before, during and after treatment with _____. Finally, the Slone Epidemiology Unit at the University of Boston School of Public Health has an ongoing survey of Accutane (isotretinoin) patients to track the safety issues related to its use.

In cases where these safety precautions are taken, it is unlikely that a patient would inadvertently receive _____ instead of another product in error. However, there may be times when these safety steps are bypassed. One worst case scenario is for a pregnant woman to receive _____ in error. Since most medications do not have recommendations for special distribution, it is more likely for a patient to receive another medication, in error, when they are prescribed _____.

Because it takes some time for _____ to be eliminated from the body, patients who receive _____ are asked to follow warnings for one month after they finish their course of therapy. Additionally, the risks can extend beyond the individual taking the medication if they were to donate blood, for example, and expose another person's baby to the effects of _____.

Loxitane and _____ may sound similar according to the expert panel. *Loxitane* and _____ share the “-tane” stem, however “LOX” is a strong sound, which may help to differentiate this name from *Isotane*. *Loxitane* is used to treat psychotic disorders, unlike _____. *Loxitane* is available as oral capsules, oral liquid concentrate and for intramuscular injection. *Loxitane* oral capsules include a 10 mg dosage strength, which overlaps with _____. There is also overlap in the dosing schedule. If a patient received *Loxitane* in error, they may experience central nervous system effects associated with *Loxitane*.

Artane and _____ can look similar according to the expert panel. Although both names share the “-tane” stem, there is less sound-alike potential since there are a different number of syllables. *Artane* is available as an oral tablet, sustained-release capsule, and elixir. *Artane* is used to treat Parkinsonism, unlike _____. Although there is no direct overlap in the dosage strengths, two 5 mg SR capsules of *Artane* could be used to make a 10 mg dose of _____. Additionally, if a prescriber uses trailing zeros for the 2 mg doses of *Artane*, (2.0 mg) it could look like 20 mg of _____ when the decimal point is not seen. If a patient received *Artane* in error, they may experience central nervous system effects associated with *Artane*.

Artane

Accutane and _____ can sound similar, however they contain the same active ingredient, isotretinoin. The risk for confusion is increased because there is overlap in dosing, dosage strengths, packaging, dosage forms, prescribers, patient population and indication. Additionally, there is potential for a patient, who does not realize that *Accutane* and _____ are the same product, to take both medications concomitantly resulting in an inadvertent overdose of isotretinoin.

Mitotane is an antineoplastic agent used to treat adrenal cortical carcinoma. The expert panel identified *mitotane* as having potential for sound-alike confusion with _____. *Mitotane* has a different indication, dosing schedule, dosing units, dosage strength, prescriber and patient population. Many institutions do not allow verbal orders for cancer chemotherapy, which may help to prevent sound-alike name confusion. If a patient received *mitotane* in error, they may experience central nervous system or gastrointestinal adverse effects associated with *mitotane*.

Isoptin can sound slightly similar to _____ because they share the “-tin” and “-in” can sound alike. Both _____ and *Isoptin* are available in a 40 mg oral dosage strength. However, *Isoptin* is used to treat a different condition and there is no overlapping dosage schedule. If confused, a patient may experience the cardiovascular effects associated with *Isoptin*.

Isophane (NPH insulin) has potential for sound-alike confusion with _____. However, *Isophane* is a type of insulin (NPH), which can be used alone or in combination to make the 70/30 insulin products. Insulin is available for injection only and used to treat a different condition than _____ decreasing the likelihood for confusion with *Isotane*. If a patient received *Isophane* insulin instead of _____ they may experience the inadvertent lowering of their blood sugar level.

According to the expert panel, *Isocaine* and _____ can sound very similar because they share the “_____” sounds at the beginning and the end of the names. However, there is low risk for confusion because *Isocaine* is available as a 1.8 mL dental cartridge for use in a dental practice setting. There is no overlap in the dosage forms, dosage strengths, dosing units or indication. Different types of specialists prescribe *Isocaine* and Isotane, further decreasing the likelihood for confusion between these products.

Four additional proprietary names were identified to have potential for confusion with _____ which were not discussed with the expert panel. These products are listed in the table below, along with the dosage forms available and usual FDA-approved dosage.

Product Name	Dosage form(s). Generic name	Usual adult dose*
_____	10 mg, 20 mg, 40 mg capsules	10 mg po BID
Prozac	fluoxetine 10 mg, 20 mg, 40 mg capsule 20 mg/5 mL liquid 90 mg weekly capsule	20 mg by mouth once daily in the morning
Isotrate ER	isosorbide mononitrate 60 mg extended release tablet	Initially, 30 mg (given as 1/2 of a 60 mg tablet) or 60 mg (one tablet) once daily. After several days, the dosage may be increased to 120 mg (given as two 60 mg tablets) once daily.
Proscar	finasteride 5 mg tablet (also 1 mg tablet as Propecia)	5 mg by mouth once daily
Ilosone	erythromycin 250 mg capsule oral suspension : 125 mg/5 mL 250 mg/5 mL	250 to 500 milligrams every 6 hours.

*Frequently used, not all-inclusive

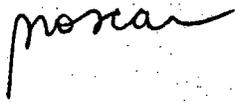
Prozac can look similar to _____. As seen below, “_____” and “Pro” can look similar when handwritten. *Prozac* is used for a different indication and has a different dosing schedule than _____. However, there is overlap in the dosage strengths of 10 mg, 20 mg and 40 mg.

prozac

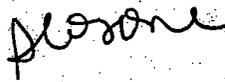
Isotrate ER can look similar to _____. *Isotrate ER* is used to treat angina pectoris and is available as a 60 mg extended-release tablet for once daily administration, unlike _____. However, it is possible to make a 60 mg dose from 20 mg and 40 mg of _____ capsules. *Isotrate ER* has a different indication, dosing schedule, decreasing the likelihood for confusion with _____.

Isotrate ER

Proscar has potential for look-alike confusion with _____ When handwritten, an '_____' can look like a "Pro". *Proscar* is used to treat benign prostatic hypertension, unlike _____. It is available as a 5 mg tablet, however it is possible to use two 5 mg tablets to make a 10 mg _____ dose. There is no overlap in the dosing schedule, further decreasing the likelihood for confusion. Both medications are classified as Pregnancy category X.



Ilosone can look similar to _____ because "ilo" is similar to '_____' and "sone" can look similar to _____". *Ilosone* is an antibiotic, used to treat various infections. Since antibiotics are frequently prescribed for severe acne, the indication, patient population and prescribers of _____ and *Ilosone* may overlap. Although there is no overlap in dosage strength, erythromycin antibiotics may be administered twice daily, similar to _____.



There were several names of products identified to have potential for confusion with _____ however these products are no longer actively marketed in the USA. These names were *Isolan* and *Isotein HN*, both were nutritional products available without a prescription. *Veltane* was an antihistamine product, which has not been manufactured for approximately ten years.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the carton labeling, container labeling and draft package insert for _____ OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. OUTPATIENT BLISTER PACK LABELS

1. Since this product is to be dispensed to a patient, please assure that the packaging is child-resistant.
2. We recommend that the sponsor modify the color of type used for the 40 mg dosage strength package. The black type on the blue background makes the dosage strength difficult to see. The most obvious number becomes the "10 Capsules" and there may be potential for confusion with the 10 mg strength _____ product.

B. INPATIENT UNIT DOSE LABELS

We encourage the differentiation of the product strengths on all the labels and labeling with the use of contrasting colors, boxing or some other means.

C. CARTON LABELS

1. See previous comment from III-A-2.
2. Please revise your labels to decrease the amount of space devoted to the corporate name and logo. We refer you to the "ASHP Guidelines on Preventing Medication Errors in Hospitals", *American Journal of Hospital Pharmacy*, Volume 50, FEB 1993, pg 305-314. Of particular interest are the Recommendations for Pharmaceutical Manufacturers and Approval organizations, item 6, which notes that important information (drug name and strength) should have the greatest prominence, and information like company names and logos should be given lesser prominence. We believe your labels devote too much space to the company name.

D. INSERT LABELING

1. BOX WARNING

- a. We note that the words "" are written directly above the first box containing the contraindications and warnings. Emphasize "" by placing it in closer proximity to the image of the pregnant woman.
- b. We note the labeling differs from innovator because this manufacturer is not going to supply pregnancy test kits. We recommend providing the pregnancy test kits and modifying the labeling as seen in the innovator labeling. Pregnancy tests are critical to the safe use of Isotane.
- c. We recommend modifying the rotation of the image of the pregnant woman to be the same as this image in the innovator's labeling. At this time, the image faces the exact opposite direction of the innovator's image.

2. WARNINGS

- a. In the Physician's Desk Reference, we note that the innovator does not combine the warning for "decreased night vision" and "Corneal Opacities". We recommend using a separate section for "decreased night vision".

3. DOSAGE AND ADMINISTRATION

- a. DOSING BY WEIGHT TABLE
 1. Use horizontal lines or shading to enhance the dosing table and facilitate reading of dosing information as you follow across the row for each weight listed. The innovator labeling uses a grid with horizontal and vertical lines.

IV. RECOMMENDATIONS

- A. OPDRA does not recommend the use of the proprietary name ~~_____~~
- B. OPDRA has no objection to the use of a proprietary name for this product.
- C. OPDRA recommends implementation of the above labeling revisions.
- D. OPDRA recommends that all manufacturers of isotretinoin promote its safe use with the same practices as the innovator, outlined in section II-C of this review.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Marci Lee at 301-827-0914.

Marci Lee B-22-01
Marci Lee, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips 8/22/01
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: ANDA 76-041

HFD-611; Peter Rickman, Acting Division Director

HFD-613; Lillie Golson, Labeling Review Branch, Office of Generic Drugs

HFD-040; Spencer Salis, Senior Regulatory Review Officer, DDMAC

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Sammie Beam, Project Manager, OPDRA

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**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: 1-9-2002

DUE DATE: 2-15-2002

ODS CONSULT #: 01-0111-2

TO: Peter Rickman
Acting Director, Division of Labeling and Program Support
Office of Generic Drugs
HFD-611

THROUGH: Harvey Greenberg, Project Manager
HFD-615

PRODUCT NAME:
____ (Primary)
____ (Alternate)
(Isotretinoin Capsules, USP)
10 mg, 20 mg, 40 mg

SPONSOR: Ranbaxy Laboratories, Ltd.

ANDA #: 76-041

SAFETY EVALUATOR: Marci Ann Lee, PharmD

SUMMARY: In response to a consult from the Office of Generic Drugs, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names _____ and _____ to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend to the use of the proprietary name _____. From a safety perspective, DMETS has no objection to the use of the proprietary name _____. However, DDMAC is concerned that the use of "_____" implies the drug is like _____ and overstates the safety of this drug.

**APPEARS THIS WAY
ON ORIGINAL**

Carol Holquist 2/15/02
Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

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Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 11, 2002

ANDA NUMBER: 76-041

NAME OF DRUG: (Primary name) (Alternate name)
(Isotretinoin Capsules, USP)
10 mg, 20 mg, 40 mg

ANDA SPONSOR: Ranbaxy Laboratories, Ltd.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION

This consult was written in response to a request from the Office of Generic Drugs, for assessment of the tradenames "" and "", regarding potential name confusion with other proprietary or established drug names. This is the second submission for a proprietary name review. The sponsor originally submitted , and DMETS did not find this acceptable (See OPDRA consult 01-0111).

PRODUCT INFORMATION

or (isotretinoin capsules, USP) is a retinoid, which is indicated for the treatment of nodular acne. Isotretinoin inhibits sebaceous gland function and keratinization. The recommended dosage for ; or is 0.5 to 2 mg/kg given in two divided doses daily for 15 to 20 weeks. or will be available as 10mg, 20 mg and 40 mg soft gelatin capsules.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference textsⁱ,ⁱⁱ as well as several FDA databasesⁱⁱⁱ for existing drug names which sound-alike or look-alike to "" OR "" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted^{iv}. The Saegis^v Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, to simulate the prescription ordering process.

ⁱ MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, PoisINDEX, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), INDEX Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-02, and online version of the FDA Orange Book.

^{iv} www location <http://tess.uspto.gov/bin/gate.exe?f=tess&state=ki4gp0.1.1>

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, ~~_____~~ and ~~_____~~. Potential concerns regarding drug marketing and promotion related to each proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns with ~~_____~~ in regard to promotional claims.
2. The Expert Panel identified two proprietary names, Zyban and Zyrtec, that were thought to have potential for confusion with ~~_____~~. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1. Potential Sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Look-alike or Sound-alike
_____	isotretinoin capsules, USP 10 mg, 20 mg, 40 mg	10 mg PO BID	
Zyban	bupropion 150 mg sustained release tablets	150 mg PO BID	Look-alike and sound-alike
Zyrtec	cetirizine 5 mg and 10 mg tablets 5 mg/5 mL syrup	5 to 10 mg PO once daily	Look-alike

* Frequently used, not all inclusive

3. DDMAC was concerned with ~~_____~~ because the use of ~~_____~~ implies the drug is like ~~_____~~ and overstates the safety of this drug, which is associated with significant risk.
4. The Expert Panel identified one proprietary name, Naqua, that was thought to have potential for confusion with ~~_____~~. This product is listed in Table 2, along with the dosage forms available and usual FDA-approved dosage.

Table 2. Potential Sound-alike and look-alike names identified by DMETS Expert Panel

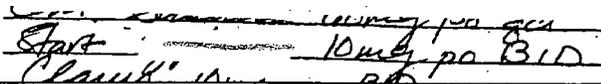
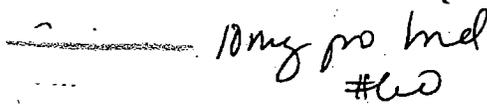
Product Name	Dosage form(s), Generic name	Usual adult dose*	Look-alike or Sound-alike
_____	isotretinoin capsules, USP 10 mg, 20 mg, 40 mg	10 mg PO BID	
Naqua	trichlormethiazide 4 mg tablets	2 to 4 mg PO once daily	Sound-alike

* Frequently used, not all inclusive

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for _____

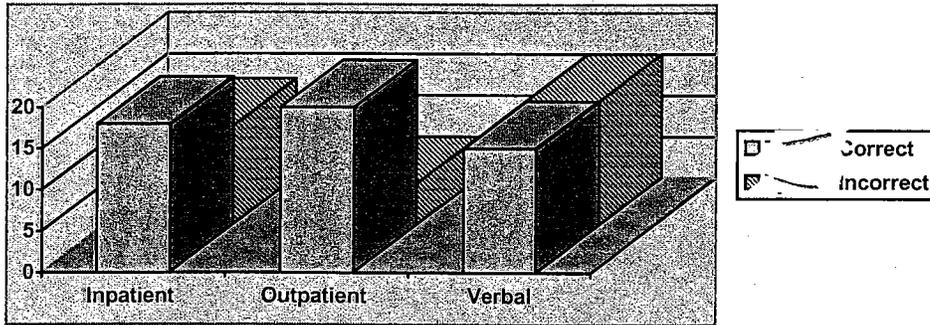
A study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of _____, with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 115 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for _____ each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Inpatient:</p> 	<p>Verbal:</p> <p>10 mg Take one twice daily. Dispense sixty.</p>
<p>Outpatient:</p> 	

2. Results for _____

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	response	Other response
Written: Inpatient	40	30 (75%)	18 (60%)	12 (40%)
Written Outpatient	35	25 (71%)	20 (80%)	5 (20%)
Verbal:	40	30 (75%)	15 (50%)	15 (50%)
Total:	115	85 (74%)	53 (62%)	32 (38%)



Among the two written prescription studies, 17 of 55 (31 %) participants interpreted the name incorrectly. The most common incorrect interpretation was *Zytone*. Other misinterpretations included *Aytane*, *Zydone*, *Zyrtane*, *Zytam*, *Zytanc*, *Zytaxime*, *Zythane* and *Zytrane*.

Among the verbal prescription study participants for _____, 15 of 30 (50 %) participants interpreted the name incorrectly. However, none of the incorrect responses were marketed products and many of the incorrect responses were phonetically equivalent to _____. Incorrect responses were *Xitane*, *Xytane*, *Ziatane*, *Ziathen*, *Zitan*, *Zitane* and *Zytain*.

3. Methodology for _____

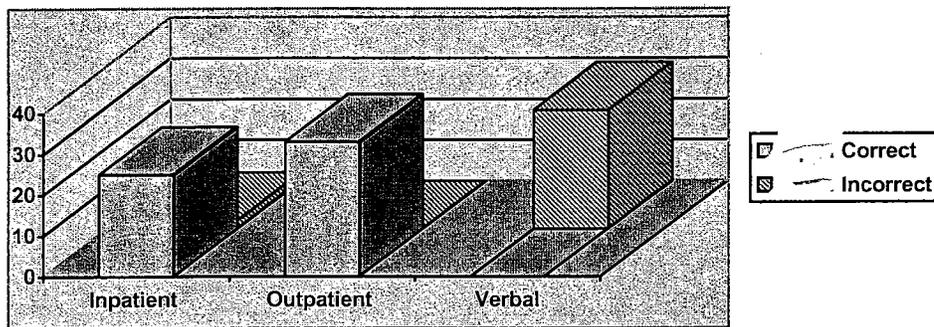
A study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of _____ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 115 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for _____, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
<p>Inpatient:</p> <p><i>Verbal, 7i 100mg of xylax. 40mg Continue (40mg po BID) Continue (40mg po BID)</i></p> <p><i>40mg</i></p> <p><i>Sig: 7po BID</i></p> <p>Outpatient: <i>#60</i></p>	<p>Verbal:</p> <p><i>40 mg</i></p> <p>Take one tablet twice daily. Dispense sixty.</p>

4. Results for _____

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	Correct response	Other response
Written: Inpatient	35	27 (77%)	25 (93%)	2 (7%)
Written Outpatient	40	33 (83%)	33 (100%)	0 (0%)
Verbal:	40	29 (73%)	0 (0%)	29 (100%)
Total:	115	89 (77%)	58 (65%)	31 (35%)



Among the two written prescription studies, 2 of 60 (3 %) participants interpreted the name incorrectly. Incorrect interpretations included _____ and _____.

Among the verbal prescription study participants for _____ 29 of 29 (100 %) participants interpreted the name incorrectly. However, all of the incorrect responses were phonetically equivalent to _____. The most common incorrect response was *Equal*. Other incorrect responses included *Equol*, *Ayqual*, *E-Kwell*, *E-Qual*, *Equale*, *Equall*, *Equell*, *Eqwal* and *Eqwall*.

C. SAFETY EVALUATOR RISK ASSESSMENT

1 _____ Assessment

In reviewing the proprietary name, _____ the primary concerns raised by the expert panel were related to two proprietary names that already exist in the US marketplace, Zyban and Zyrtec. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that _____ could be confused with Zyban or Zyrtec. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Although no one interpreted the name as either Zyban or Zyrtec, one respondent interpreted the name as Zydone, which is a currently approved drug name in the US marketplace.

Zydone has potential for both look-alike and sound-alike confusion with _____: Zydone is a narcotic analgesic product marketed in the US. Unlike _____, Zydone is a combination product containing hydrocodone and acetaminophen, which is available in three different dosage strengths. Zydone has a different indication and a different dosing schedule than _____ which minimizes the confusion potential. Zydone is typically used for up to 10 days to relieve moderate to severe pain on an as needed basis. In addition Zydone may be stored with other controlled substances in some pharmacies, which may help to decrease the risk for confusion. Although there is significant look-alike similarity between these names, the clinical context differs so much that the risk for confusion is minimal.

_____ zydone _____ 10mg pro bid #60

Zyban was identified to have potential for look-alike and sound-alike confusion. Both Zyban and _____ share the "_____", the same number of syllables and a similar ending sound with "____". The look-alike confusion is mainly due to similar letters (z, y, a, n) and the upstroke of the "____" and "b" appear in the middle portion of the names. Zyban has a different indication than _____. It is used to aid patients in smoking cessation. Zyban is available as a 150 mg oral sustained release tablet, which further minimizes the likelihood for confusion with _____. However, Zyban and _____ are both used for periods of seven to twelve weeks or 15 to 20 weeks, respectively. They share a common frequency of administration, twice daily. Both medications will be used mostly on an outpatient basis. However, it is likely that different specialists would prescribe these medications. Since both names start with "____", it is also possible for these medications to be stored near each other on a pharmacy shelf, depending on how medications are organized. If confusion did occur between Zyban and _____, the patient would be exposed to potentially harmful effects associated with each. _____ carries a risk to pregnant women and Zyban carries a risk that affects seizure threshold.

_____ zyban

The expert panel identified Zyrtec to have potential for look-alike confusion with _____. Both names contain "____", the letter "____" and the same number of letters. Additionally, the letter "____" and "c" can look similar at the end of the names. However, the clinical context of use for each medication is very different and the only similarity is that both medications are available as 10 mg oral solid dosage forms. Additionally, Zyrtec and _____ will be used mostly on an outpatient basis. It is also possible that they would be stored near each other on a pharmacy shelf.

_____ zyrtec

Extain is a proposed proprietary name for an extended release formulation of oxycodone that may come to market in the near future. DMETS found this name to be acceptable upon initial and final review. See OPDRA consults 00-0317 and 01-0114. There may be potential for sound-alike confusion between Extain and _____, especially if they are introduced at the same time.

2. Assessment

In reviewing the proprietary name, [redacted], the primary concerns raised by the expert panel were related to one proprietary name that already exists in the US marketplace, Naqua. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that [redacted] could be confused with Naqua. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Naqua has the potential for sound-alike confusion with [redacted]. Naqua is used to treat hypertension, unlike [redacted]. It is available as a 2 mg and 4 mg oral tablet, which can be confused with 20 mg or 40 mg of [redacted] if written with a trailing zero as 2.0 mg or 4.0 mg. Both Naqua and [redacted] are administered twice daily. However, Naqua was launched in 1965 and its use has fallen since the newer thiazide diuretics have come to market. This may help to minimize the risk for confusion with [redacted].

III. COMMENTS TO BE PROVIDED TO THE SPONSOR

The primary concern with [redacted] was related to potential for look-alike and sound-alike confusion with Zyban. Both Zyban and [redacted] share the [redacted] the same number of syllables and a similar ending sound with [redacted]. The look-alike confusion is mainly due to similar letters [redacted] and the upstroke of the [redacted] and "b" appear in the middle portion of the names. Zyban has a different indication than [redacted]. It is used to aid patients in smoking cessation. Zyban is available as a 150 mg oral sustained release tablet, which further minimizes the likelihood for confusion with [redacted]. However, Zyban and [redacted] are both used for periods of seven to twelve weeks or 15 to 20 weeks, respectively. They share a common frequency of administration, twice daily. Both medications will be used mostly on an outpatient basis. However, it is likely that different specialists would prescribe these medications. Since both names start with [redacted], it is also possible for these medications to be stored near each other on a pharmacy shelf, depending on how medications are organized. If confusion did occur between Zyban and [redacted], the patient would be exposed to potentially harmful effects associated with each. [redacted] carries a risk to pregnant women and Zyban carries a risk that affects seizure threshold.

[redacted] Zyban

Zyrtec also has potential for look-alike confusion with [redacted]. Both names contain [redacted], the letter [redacted] and the same number of letters. Additionally, the letter [redacted] and "c" can look similar at the end of the names. However, the clinical context of use for each medication is very different and the only similarity is that both medications are available as 10 mg oral solid dosage forms. Additionally, Zyrtec and [redacted] will be used mostly on an outpatient basis. It is also possible that they would be stored near each other on a pharmacy shelf.

[redacted] Zyrtec

IV. LABELING, PACKAGING AND SAFETY RELATED ISSUES

See previous comments from [redacted] review (Consult 01-0111).

V. RECOMMENDATIONS

- A. DMETS does not recommend the use of the proprietary name " ———"
- B. DMETS has no objection to the use of the proprietary name ———. However, DDMAC is concerned that the use of " ———" implies the drug is like ——— and overstates the safety of this drug.

This is considered a tentative decision and the firm should be notified that this name with its labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

 2-15-02

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-041

HFD-615; Harvey Greenberg, Project Manager

Electronic only cc:

HFD-610; Peter Rickman, Acting Division Director

HFD-613; Lille Golson, Labeling Review Branch

HFD-400; Marci Lee, Safety Evaluator, DMETS

HFD-400; Sammie Beam, Project Manager, DMETS

L:\ODS02\LEE\01-0111-2ZYTANEandAQUALFIN.DOC

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

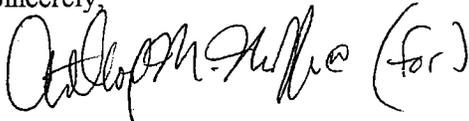
76-041

CORRESPONDENCE

As indicated as acceptable by Ms. Dillahunt on December 16, 2002, Ranbaxy Laboratories Limited commits to make these listed changes in accordance with Office of Generic Drugs recommendations, prior to commercializing Sotret™ (Isotretinoin Capsules) 10mg, 20mg and 40 mg. Ranbaxy Laboratories Limited commits to providing the Office of Generic Drugs copies of all labeling reflecting these changes prior to commercialization as well.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony M. Maffia, III (for)". The signature is written in a cursive style with some loops and flourishes.

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

**APPEARS THIS WAY
ON ORIGINAL**

RANBAXY

LABORATORIES LIMITED

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

December 2, 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

LABELING AMENDMENT
TO PENDING APPLICATION

RE: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg
ANDA 76-041

N/A

Dear Sir/Madam:

Reference is made to pending ANDA 76-041 for Isotretinoin Capsules, USP, 10 mg, 20mg and 40 mg submitted on November 30, 2000. Reference is also made to telephone contact from Ms. Michelle Dillahunt, OGD on November 6, 2002 and the fax and email follow-ups.

This labeling amendment is being submitted in order to present one additional piece of labeling for use with *I.M.P.A.R.T.*, Ranbaxy's Risk Management Program for Isotretinoin Capsules. As requested by telephone, fax and email contact with Michelle Dillahunt at the OGD, Ranbaxy is submitting the *Pharmacy Dispensing Guide*, a wall hung poster for Pharmacists, detailing the dispensing procedures for Sotret™ (Isotretinoin Capsules). The *Pharmacy Dispensing Guide* also contains two detachable telephone reference cards as created by Roche Pharmaceuticals for use with Accutane®. The dispensing Guide may be found in Attachment 1.

We have preserved all portions of the RLD labeling that are accurate in regards to the Sotret Resource Center, however due to differences in operation there are differences (i.e. the Roche automated telephone line is support for both Accutane and Soriatane® and the Ranbaxy telephone line has more live operator supported functions rather than teleprompting). A side by side comparison using color to highlight the differences between Ranbaxy's Dispensing Guide and that of Roche are included to facilitate review. This side by side presentation is found in Attachment 2.

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

RECEIVED

DEC 03 2002

OGD / CDER

RANBAXY
LABORATORIES LIMITED

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

November 11, 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

LABELING AMENDMENT
TO PENDING APPLICATION

ORIGINAL AMENDMENT

**RE: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg
ANDA 76-041**

N/AF

FPL

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, USP, 10 mg, 20mg and 40 mg submitted on November 30, 2000. Reference is also made to the most recent labeling amendments submitted August 5, 2002 and August 9, 2002. Lastly, reference is made to the FDA labeling deficiency received by fax October 23, 2002.

Provided on the following pages are the Agency's deficiencies followed by Ranbaxy's response. Twelve sets of the final printed labeling are included in **Attachment 1**. Please note, the appropriate number of I.M.P.A.R.T. brochures have been included, but have not been bound in the submission as requested in telephone conversation with Miss Michelle Dillahunt. These brochures have been labeled with a single page number on the front of each booklet for easy reference as in previous submissions.

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, for your reference, in **Attachment 3**, an actual blister pack which will illustrate that the blister pack does contain a child resistant closure. We have provided a copy of our educational video script with the revised title, *Always Careful, Always Ready*, in **Attachment 4**.

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 revised proposal with changes based on that conversation is included in **Attachment 5**.

RECEIVED

NOV 12 2002

OGD/CDER

ANDA 76-041
Labeling Amendment
November 11, 2002

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* as indicated in the attached comments. 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.

This amendment is being submitted in one volume.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony M. Maffia, III (for)". The signature is written in a cursive style with a large initial "A" and a circled "for" at the end.

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

August 9, 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

FPL

LABELING AMENDMENT
TO PENDING APPLICATION

RE: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg
ANDA 76-041

ORIG AMENDMENT
N/AF

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, USP, 10 mg, 20mg and 40 mg submitted on November 30, 2000. Reference is also made to the labeling amendments submitted December 20, 2001, May 3, 2002 and August 5, 2002.

This labeling amendment is being submitted in order to present additional items of Ranbaxy's isotretinoin capsules labeling program as requested by OGD. As requested by telephone and email contact with Lillie Golson at the OGD, Ranbaxy is submitting final copies of labeling components that are necessary in order to facilitate review. Please note, Ranbaxy is submitting only two copies of each of these components as instructed in our discussions with Ms. Golson.

Ranbaxy is submitting a Pharmacy Compliance Survey protocol proposal as requested by OGD. A copy of the email correspondence from Ms. Lillie Golson describing the necessary components of this survey is also included for reference. These items may be found in **Attachment 1**.

This amendment contains copies of the proposed letters to both Prescribers and Dispensers of Isotretinoin Capsules alerting them to the details of I.M.P.A.R.T, Isotretinoin Medication Program Alerting the Risks of Teratogenicity, Ranbaxy's risk management program that is based on and comparable to Roche Lab's S.M.A.R.T. Program for use with Accutane®. These may be found in **Attachments 2 & Attachment 3** respectively.

Attachment 4 contains the a copy of the program algorithm for I.M.P.A.R.T, Ranbaxy's risk management program, in flowchart form.

RECEIVED

AUG 12 2002

OGD / CDER

ANDA 76-041
Labeling Amendment
August 9, 2002

Please note, that due to unforeseen trademark issues, Ranbaxy's previously submitted risk management program name, C.L.A.R.I.T.Y (an acronym for *Control and Awareness of Risk of Isotretinoin Teratogenicity*) has been replaced with I.M.P.A.R.T. (*an acronym for Isotretinoin Medication Program Alerting the Risks of Teratogenicity*). This new name is reflected in all the components submitted in this amendment.

This amendment is being submitted in one volume.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Anthony M. Maffia, III" followed by a circled "for" in parentheses.

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

N/A=

August 5, 2002

ORIG AMENDMENT

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

**LABELING AMENDMENT
TO PENDING APPLICATION**

**RE: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, USP, 10 mg, 20mg and 40 mg submitted on November 30, 2000. Reference is also made to the labeling amendment submitted December 20, 2001. Reference is also made to the labeling amendment submitted May 3, 2002.

This labeling amendment is being submitted in order to present Ranbaxy's isotretinoin capsules labeling program in a complete form as requested by OGD. As requested by telephone and email contact with Lillie Golson at the OGD, Ranbaxy is submitting final copies of labeling components that are necessary in order to facilitate review. Please note, Ranbaxy is submitting only two copies of each of these components as instructed in our discussions with Ms. Golson. This amendment contains printed desk copies of the four brochures that will make up I.M.P.A.R.T, Isotretinoin Medication Program Alerting the Risks of Teratogenicity, Ranbaxy's risk management program that is based on and comparable to Roche Lab's S.M.A.R.T. Program for use with Accutane®. A detailed outline of which components are included in each of these brochures is included in the following pages. Upon approval of these labeling components, additional final copies will be made available to the OGD.

Reference is also made to the FDA correspondence for Roche Lab's Accutane® (isotretinoin capsules), NDA 18-662, Supplements S-041, S-043, S-044, S-045, S-046, S-047 and S-051. A summary of this FDA correspondence is provided.

Ranbaxy is also submitting updated copies of blister card labeling, carton labeling, the package insert, the medication guide and patient informed consent forms incorporating the approved changes from the above cited Roche Labs supplemental applications.

RECEIVED

AUG 06 2002

OGD / CDER

ANDA 76-041
Labeling Amendment
August 5, 2002

Ranbaxy has previously submitted proprietary names for the isotretinoin capsules. A summary of the names submitted is provided. The names Sotret _____ and _____ were submitted in the labeling amendment dated May 3, 2002 and Lillie Golson, from the OGD, has made Ranbaxy aware that Sotret and _____ have been forwarded to OPDRA for review. Representative labeling for the carton and blister packaging have been forwarded in this amendment for the established name as well as the names Sotret _____ and _____

Due to unforeseen trademark issues, Ranbaxy's previously submitted risk management program name, C.L.A.R.I.T.Y (an acronym for *Control and Awareness of Risk of Isotretinoin Teratogenicity*) has been replaced with I.M.P.A.R.T. (*an acronym for Isotretinoin Medication Program Alerting the Risks of Teratogenicity*). This new name is reflected in all the components submitted in this amendment.

This amendment is being submitted in two volumes.

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

July 15, 2002

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

MINOR AMENDMENT
FAX & UPS OVERNIGHT

ORIGINAL AMENDMENT
N/Am

Reference: ANDA 76-041
Isotretinoin, Capsules, 10 mg, 20 mg & 40 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin, Capsules, 10 mg, 20 mg & 40 mg submitted November 30th, 2000.

Reference is also made to the FDA's minor deficiency letter dated June 12, 2002.

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

We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this submission has been provided to the Food and Drug Administration, New Jersey District Office in Parsippany, New Jersey.

If you have any questions regarding this submission, please call me at (609)-720-5336 or Ms. Abha Pant at (609) 720-5666.

Sincerely,



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

RECEIVED

JUL 17 2002

OGD / CDER



RANBAXY
LABORATORIES LIMITED

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

June 5, 2002

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

UPS & FAX

**BIOEQUIVALENCE COMMENTS
ACKNOWLEDGEMENT**

**RE: ISOTRETINOIN CAPSULES USP, 10 mg, 20 mg & 40 mg
ANDA 76-041**

ORIG AMENDMENT

NC/B10

Dear Sir/Madam:

Reference is made to the above pending ANDA 76-041 for Isotretinoin Capsules USP, 10 mg, 20 mg & 40 mg and the attached Bioequivalence Comments letter from the OGD dated May 1, 2002.

Ranbaxy acknowledges receipt of the following bioequivalence comments and will incorporate the indicated dissolution testing into both our stability and quality control programs.

The dissolution testing should be conducted in

**The test products should meet the following
specification:**

**Not less than (Q) of the labeled amount of the drug in the
dosage form is dissolved in 90 minutes (interim).**

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

Sincerely,

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

RECEIVED

JUN 06 2002

OGD / CDER

RANBAXY
LABORATORIES LIMITED

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

May 16, 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

FAX AND UPS

AMENDMENT TO A PENDING
APPLICATION

N/A

RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg.

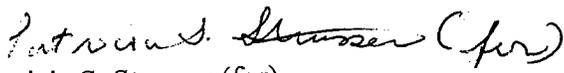
Reference is also made to the Bioequivalency comments of May 1, 2002. The Division of Bioequivalence has completed their review and specified the dissolution testing parameters that should be incorporated into our stability and quality control programs.

Ranbaxy is amending the application for ANDA 76-041 to include the final specifications and test methods for dissolution.

FIELD COPY: This is to certify that the field copy is a true copy of the technical sections described in the 21 CFR 314.94(d)(5). Chemistry, manufacturing and controls section contained in the archival and review copies of the application.

If further information is necessary, please call Abha Pant at 609-720-5666. Thank you.

Sincerely,


Patricia S. Strasser (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED

MAY 20 2002

OGD / CDER

RANBAXY
LABORATORIES LIMITED

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

April 1, 2002

NLAB

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

FAX AND UPS

ORIG AMENDMENT

BIOEQUIVALENCE

TELEPHONE AMENDMENT

RE: Isotretinoin Capsules 10 mg, 20 mg and 40 mg
ANDA 76-041

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules 10 mg, 20mg and 40 mg.

Reference is also made to the telephone deficiency of March 21, 2002.

Ranbaxy's response to the deficiency questions is in the same order as requested.

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 Office of Generic Drugs for FDA's International Operations Group.

If further information is necessary, please call Abha Pant at 609-720-5666. Thank you.

Sincerely,

Abha Pant
Abha Pant

US Agent for Ranbaxy Laboratories Limited

RECEIVED

APR 03 2002

OGD / CDER

RANBAXY
LABORATORIES LIMITED

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

February 15, 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

FAX AND UPS

NE to Bio
NEW CORRESP

**ADDITIONAL INFORMATION
FOR THE BIOEQUIVALENCE
& MINOR AMENDMENT
RESPONSE DATED 2/4/02**

**RE: Isotretinoin Capsules 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules 10 mg, 20mg and 40 mg. Reference is also made to our response dated February 4, 2002 to the Agency's Bioequivalence and Minor Deficiencies.

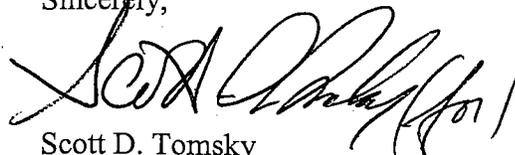
In our response to the Agency's deficiency questions we failed to make reference to the Agency's Bioequivalence Deficiency letter dated December 28, 2001. On page 0005 of our response, the heading under section C refers to the Division of Bioequivalence deficiencies. In this heading we only mentioned the phone contact of December 18, 2001 and failed to mention the letter received December 28, 2001, which identified the questions addressed in our response. Please accept this additional information to supplement our response to these questions dated February 4, 2002. In addition, we have enclosed a copy of the Bioequivalence Deficiency letter dated December 28, 2001.

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 Office of Generic Drugs for FDA's International Operations Group.

If further information is necessary, please call Abha Pant at 609-720-5666. Thank you.

Sincerely,



Scott D. Tomsky
Regulatory Affairs Associate (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

February 4, 2002

ORIG AMENDMENT
N/AM.

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

FAX AND UPS

BIOEQUIVALENCE &
MINOR AMENDMENT

**RE: Isotretinoin Capsules 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules 10 mg, 20mg and 40 mg. Reference is also made to the telephone conversation of December 18, 2001 with the Division of Bioequivalence, and the Minor Amendment deficiency dated January 9, 2001.

2062

Ranbaxy's response to the deficiency questions is in the same order as requested.

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 Office of Generic Drugs for FDA's International Operations Group.

If further information is necessary, please call Pat Strasser at 609-720-5617 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsy (for)

Scott D. Tomsy
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited



*MD
2/2/02*

RANBAXY
LABORATORIES LIMITED

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

December 20, 2001

ORIG AMENDMENT
N/AF

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

**LABELING AMENDMENT
TO PENDING APPLICATION**

**RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg. Reference is also made to NDA 18-662/S-044 for Accutane® (isotretinoin) capsules 10 mg, 20 mg and 40 mg. The labeling supplement for NDA 18-662 was posted on the FDA website in November of 2001.

The supplement for NDA 18-662/S-044 provided for revisions to the labeling to reflect the System to Manage Accutane® Related Teratogenicity (S.M.A.R.T.) Program, an enhanced risk management program to prevent fetal exposure to Accutane®.

Ranbaxy is submitting this labeling amendment to reflect the changes in the innovator labeling for Accutane®.

A summary of the labeling in this amendment is provided.

If you have any additional questions, please call me at 609-720-5617 or Abha Pant at 609-720-5666.

Sincerely,

Pat Strasser (for)
Pat Strasser (for)
Abha Pant
U.S. 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

BIOEQUIVALENCY

NEW CORRESP

NC

December 5, 2001

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

FAX AND UPS

AMENDMENT TO THE
BIOEQUIVALENCY AMENDMENT

RE: Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg
ANDA 76-041

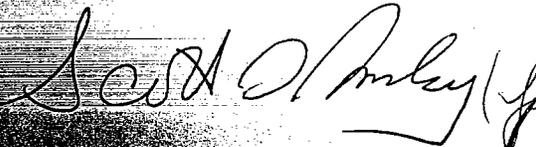
Dear Sir/Madam:

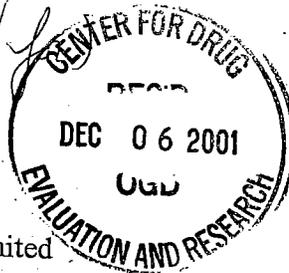
Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules USP 10 mg, 20mg and 40 mg. Reference is also made to the Bioequivalency Amendment response dated December 4, 2001.

We want to amend the information provided on page 3 of the response dated December 4, 2001, we inadvertently listed the lot # in the question and response to #1 as 03584 rather than U3584. Please replace the original page with the revised page provided in this amendment.

If further information is necessary, please call me at 609-720-5666. Thank you.

Sincerely,


Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited



RANBAXY

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

December 4, 2001

N/AB

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

FAX AND UPS

ORIG AMENDMENT

BIOEQUIVALENCY AMENDMENT

**RE: Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules USP 10 mg, 20mg and 40 mg. Reference is also made to the Bioequivalency Amendment deficiency dated November 6, 2001.

Ranbaxy's response to the deficiency questions are in the same order as requested.

If further information is necessary, please call me at 609-720-5666. Thank you.

Sincerely,



Abha Pant

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

December 11, 2001

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

**LABELING AMENDMENT
TO PENDING APPLICATION
ORIG AMENDMENT**

N/A

**RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg. Reference is also made to the correspondence of August 15, 2001 requesting the addition of the trade name _____

Reference is also made to the telephone contact of December 10, 2001, requesting that the name _____ be withdrawn.

Ranbaxy is requesting withdrawal of the _____ brand name for Isotretinoin Capsules, ANDA 76-041. We are hereby withdrawing the name of _____ without prejudice to any future filing to this application.

If you have any additional questions, please call me at 609-720-5617 or Abha Pant at 609-720-5666.

Sincerely,

Patricia S. Strasser (for)
Patricia S. Strasser (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 15, 2001

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

FAX AND UPS

MINOR AMENDMENT

ORIG AMENDMENT

N/A M

**RE: Isotretinoin Capsules 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules 10 mg, 20mg and 40 mg. Reference is also made to the Minor Amendment deficiency dated October 3, 2001.

Ranbaxy's response to the deficiency questions is in the same order as requested.

Field Copy:

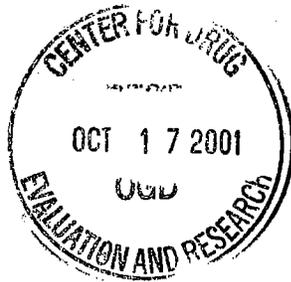
We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this amendment has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If further information is necessary, please call Pat Strasser at 609-720-5617 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Stephanie Davis

Stephanie J. Davis
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited



*MS
10/19/01*

RANBAXY

LABORATORIES LIMITED

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

September 21, 2001

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

FAX AND UPS

BIOEQUIVALENCY AMENDMENT

BIOAVAILABILITY

ORIG AMENDMENT

N/A/B

RE: **Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg**
ANDA 76-041



Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules USP 10 mg, 20mg and 40 mg. Reference is also made to the Bioequivalency Amendment deficiency dated June 20, 2001.

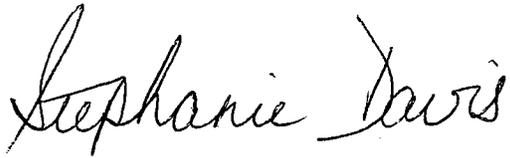
Ranbaxy's response to the deficiency questions is in the same order as requested.

Also, please note that the additional Fasting Biostudy, requested by the Division of Bioequivalence is included as Attachment 3 of the response. The biostudy attachment is provided as follows:

Volume 1	Pages 0028-0498
Financial Certifications	Pages 0028A-0028I
Diskette of randomization	Attached to Front Cover
Printout of Randomization	Attached to Front Cover
Volume 2	Pages 0499-0960
Volume 3	Pages 0961-1453
Volume 4	Pages 1454-1929

If further information is necessary, please call me at 609-720-5623 or Abha Pant at 609-720-5666. Thank you.

Sincerely,



Stephanie J. Davis
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited



**APPEARS THIS WAY
ON ORIGINAL**

RANBAXY

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

August 15, 2001

NEW CORRESP

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

**LABELING AMENDMENT
TO PENDING APPLICATION**

**RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg.

The labeling submitted in the original ANDA for Isotretinoin Capsules was submitted with the trade name . Ranbaxy Laboratories Limited is submitting an additional trade name. The additional trade name is and this is the preferred name.

After the labeling comments are received from OGD, Ranbaxy will submit final printed labeling with the preferred trade name

If you have any additional questions, please call me at 609-720-5617 or Stephanie Davis at 609-720-5623.

Sincerely,

Patricia S. Strasser

Patricia S. Strasser (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited



RANBAXY

LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

July 17, 2001

N/AM

ORIG AMENDMENT

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

FAX AND UPS

MINOR AMENDMENT

**RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg.

Reference is also made to the Minor Amendment deficiency dated May 18, 2001.

Ranbaxy's response to the deficiency questions is in the same order as requested.

Also, please note that the additional Fasting Biostudy, requested by the Division of Bioequivalence on June 20, 2001, was started last week. We will respond to the Bioequivalency Deficiency as soon as we receive the Biostudy report.

FIELD COPY: This is to certify that the field copy is a true copy of the technical sections described in the 21 CFR 314.94(d)(5). Chemistry, manufacturing and controls section contained in the archival and review copies of the application.



MW
7-23-01

If further information is necessary, please call me at 609-720-5623 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Stephanie Davis". The signature is written in black ink and is positioned above the typed name.

Stephanie J. Davis (for)

Shirley Ternyik

US Agent for Ranbaxy Laboratories Limited

**APPEARS THIS WAY
ON ORIGINAL**

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

NATI
"Labeling"
NC [Signature]
5/31/01
NEW CORRESP

April 19, 2001

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 OVERNIGHT AND FAX

CONTROLLED CORRESPONDENCE

**RE: Isotretinoin Capsules 10 mg, 20 mg and 40 mg
ANDA 76-041**

Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules 10 mg, 20mg and 40 mg. Reference is also made to the Roche Laboratories Literature/Booklet for Accutane® that is part of the 'Pregnancy Prevention Program for Women on Accutane®' and the list of available literature (refer to **Attachment-1, pages 4-5 of Roche's booklet**).

Many of the listed items have not been submitted as part of the labeling section in our original application.

Of the following items listed, does Ranbaxy also have to submit a comparable piece for:

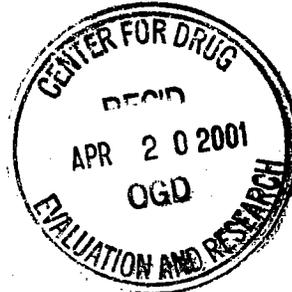
- Patient Qualification Checklist
- Patient Self-Evaluation Form
- The Roche Patient Referral Program
- AlertLine
- Video (titles 'Be Prepared, Be Protected')
- Free Urinary Pregnancy Test Kits

If further information is necessary, please call me at 609-720-5623 or Shirley TERNYIK at 609-720-5612. Thank you.

Sincerely,

Stephanie J. Davis

Stephanie J. Davis
Manager Regulatory Affairs (for)
Shirley TERNYIK
US Agent for Ranbaxy Laboratories Limited



[Handwritten initials/signature]
4/20/01

ANDA 76-041

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

JAN 11 2001

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.

Reference is made to the telephone conversation dated January 9, 2001 and your correspondence dated January 10, 2001.

NAME OF DRUG: Isotretinoin Capsules USP, 10 mg, 20 mg and 40 mg

DATE OF APPLICATION: November 30, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 4, 2000

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:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

January 10, 2001

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

FAX AND UPS

NEW CORRESP

NC

**ADDITIONAL INFORMATION
TO A PENDING APPLICATION**

**RE: Isotretinoin Capsules, 10 mg, 20 mg and 40 mg
ANDA 76-041**

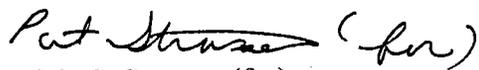
Dear Sir/Madam:

Reference is made to the pending ANDA 76-041 for Isotretinoin Capsules, 10 mg, 20mg and 40 mg. Reference is also made to a telephone request by OGD, on January 9, 2001 for additional information needed for the pending application.

Attached are copies of the FDA Forms 3454 for Study numbers 001182 and 001183, replacement pages 0097 and 0098. The sponsor's box has been checked. Also attached is an original copy of the US Agent letter, page 3797 which was missing from the original submission.

If further information is necessary, please call me at 609-720-5617 or Shirley Ternyik at 609-720-5612. Thank you.

Sincerely,


Patricia S. Strasser (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited



RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

76-041

November 30, 2000

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

UPS

505(j)(2)(A) OK
11 JAN-2001
Regency

Reference: **Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg**
Abbreviated New Drug Application

Dear Sir/Madam:

Ranbaxy Laboratories Ltd. (RLL) herewith submits an abbreviated new drug application (ANDA) for Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

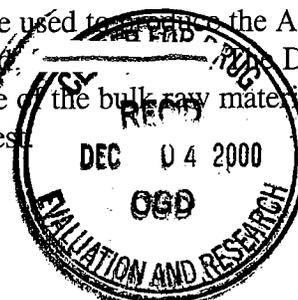
This ANDA refers to the listed drugs, Accutane® (Isotretinoin) Capsules 10 mg, 20 mg and 40 mg which are manufactured by Roche Laboratories, the holder of NDA 18-662, and as listed in the 2000 Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition, p. 3-200.

With respect to U.S. patent no. 4,464,394, the applicant certifies that in the opinion and to the best of its knowledge, the said patent will expire on August 7, 2001. Ranbaxy Laboratories Limited requests approval of this ANDA effective after August 7, 2001. In addition, no marketing exclusivities have been granted to this product.

The drug product manufacturer is Ranbaxy Laboratories Limited. Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg will be manufactured at Ranbaxy Laboratories Limited's FDA registered and inspected facility in accordance with 21 CFR 210 and 211.

The drug product will also be packaged in bulk and blister packs at the facility.

The manufacturer of the Isotretinoin USP drug substance used to manufacture the ANDA batches of drug product is Ranbaxy Laboratories Limited. Drug Master File was filed on November 29, 2000. A sample of the bulk raw material is available and will be provided to the Agency upon request.



Food and Drug Administration
Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg
Abbreviated New Drug Application
Page 2

The required bioavailability/bioequivalence study was conducted on Isotretinoin Capsules USP 40 mg and Accutane® Capsules 40 mg by ~~_____~~

~~_____~~ The study indicates that Isotretinoin Capsules USP 40 mg are bioequivalent to Accutane® Capsules 40 mg. The *in-vitro* dissolution profiles for Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg are comparable to those of Accutane® Capsules 10 mg, 20 mg and 40 mg. Therefore, a waiver of in-vivo bioavailability/bioequivalence study requirements for Isotretinoin Capsules USP 10 mg, and 20 mg is requested.

Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C/75% relative humidity).

The dosage form, route of administration, indications and usage, dosage and route of administration, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED sections) for Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg are the same as those for Accutane® Capsules USP 10 mg, 20 mg and 40 mg.

This ANDA is submitted in thirteen volumes :

Volume I:	Section I through Section V
Volume II: through Volume IX	Section VI
Volume X:	Section VII through Section XI
Volume XI:	Section XII through Section XIV
Volume XII:	Section XV
Volume XIII:	Section XVI through Section XXII

Food and Drug Administration
Isotretinoin Capsules USP 10 mg, 20 mg and 40 mg
Abbreviated New Drug Application
Page 3

Ranbaxy Laboratories Limited commits to resolve any issues identified in the methods validation process after approval.

Please contact the undersigned at 609-720-5612 if you have any questions regarding this submission.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(5) of this submission has been provided to the Office of Generic Drugs for the International Operations Group.

Sincerely,

A handwritten signature in cursive script that reads "Shirley Ternyik".

Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited.