CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-662 / S-056

Trade Name: Accutane

Generic Name: (isotretinoin)

Sponsor: Hoffman La Roche Inc.

Approval Date: August 12, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-056

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Final Printed Labeling	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-056

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-662/S-056

Hoffman La-Roche
Attention: Ellen Carey, Senior Program Manager
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms Carey:

Please refer to your pending supplemental new drug application submitted June 24, 2005, received June 27, 2005 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) Capsules, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated July 1, July 14, July 21, July 26, July 28, July 29, August 2, August 3, August 5, August 9, and August 11, 2005.

This supplemental application, considered for approval under 21 CFR 314.520 (Subpart H), at your request because of the teratogenicity of isotretinoin, proposes the iPLEDGE program, an enhanced risk minimization action plan (RiskMAP) designed to minimize drug exposure during pregnancy.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to approve the supplemental application for Accutane (isotretinoin) Capsules, 10mg, 20mg, and 40mg. You have indicated your agreement with approval under 21 CFR 314.520 (Subpart H). Accordingly, this supplemental application is approved under 21CFR 314.520 (Subpart H). Approval is effective on the date of this letter for use as recommended in the agreed upon labeling and the components of the iPLEDGE RiskMAP.

Accutane RiskMAP

We remind you that your Accutane RiskMAP (called iPLEDGE) is an important part of the postmarketing risk management for Accutane, and must include each of the following components:

1. Registration in the iPLEDGE program of wholesalers, prescribers, pharmacies, and patients who agree to accept specific responsibilities in order to distribute, prescribe, dispense, and use Accutane.
2. Implementation of a program and distribution of materials to educate wholesalers, prescribers, pharmacists, and patients about the risks and benefits of Accutane.
3. Implementation of a reporting and data collection system for: 1) serious adverse events associated with the use of Accutane that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) and 2) sales and dispensing of Accutane outside of the iPLEDGE program.
4. Implementation of a plan to monitor, evaluate, and improve minimization of drug exposure during pregnancy and compliance with restrictions for safe use under the iPLEDGE program.

A component of the evaluation program includes a pregnancy registry to elucidate the root cause of potential RiskMAP failure.

The iPLEDGE program, as described in the attached documents, adequately addresses each of these requirements. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA's determination that the required components continue to be met. We expect your continued cooperation to resolve any problems regarding the iPLEDGE program that may be identified following approval of this supplement.

We remind you of your specific reporting obligations regarding serious adverse events in patients who have received Accutane. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will submit a 15-day report for each of the following:

- All pregnancy exposures to Accutane; and
- All psychiatric events including suicides, attempted suicides, and suicidal ideation

Within the first year of initiation of the iPLEDGE program, and at the specified time frames thereafter, in addition to the Periodic Adverse Drug Experience Report required under 21 CFR 314.80(c), you must provide FDA with the following reports that will evaluate the success of the program in achieving program goals and compliance with program restrictions and requirements.

1. Special Pregnancy Periodic Quarterly Report: A quarterly report that provides information on U.S. maternal and fetal exposures to Accutane.
2. iPLEDGE Program Evaluation Report: A quarterly report that includes evaluation of program components and the rate of compliance with each in accordance with the Process Compliance Evaluation Plan discussed below, including sponsor adherence to restrictions of drug distribution to registered wholesalers, oversight of wholesaler, prescriber, pharmacy and patient compliance with relevant program requirements, and oversight of the iPLEDGE data base.
3. Non-Compliant Distribution Reports: Special reports submitted to the Division of Compliance Risk Management and Surveillance for each known occurrence during the interval since the last Program Evaluation report of: a) sale of any Accutane product by a wholesaler to an unregistered and/or un-activated pharmacy or unregistered wholesaler, b) dispensing of any Accutane product by an unregistered and/or un-activated pharmacy, and c) corrective action taken by Hoffman La-Roche for each occurrence under a) and b). These reports will be submitted within 15 days of the sponsor's receipt of new information to the following address:

   Division of Compliance Risk Management and Surveillance (HFD-330)
   Office of Compliance
   Center for Drug Evaluation and Research
   Food and Drug Administration
   5600 Fishers Lane
   Rockville, MD 20857

The content of the reports, objectives and plans for evaluation, and correction of noncompliant behavior are further described in the attached "Accutane Risk Minimization Action Plan: Summary of iPLEDGE".

To further assist FDA in evaluating any reported adverse events associated with the use of Accutane and to assist FDA in evaluating the success of the iPLEDGE program in preventing exposure of the drug in pregnant women, the Annual Periodic Adverse Drug Experience Report [required under 314.80(c)(2)], the Psychiatric Quarterly Report, the Special Pregnancy Report, and the iPLEDGE Program Evaluation Report will be submitted on the harmonized schedule below. The harmonized time frames are based on the date of mandatory compliance with the iPLEDGE program, December 31, 2005. It is understood that the initial reports may not represent a full calendar quarter or year, as appropriate. The following chart provides the harmonized specific quarterly and annual time periods for these reports:

	Reporting Period: Quarterly Reports
Quarter 1	January 1 – March 31 *(the first report for 2006 will cover December 31, 2005 – March 31, 2006)*
Quarter 2	April 1 – June 30
Quarter 3	July 1 – September 30
Quarter 4	October 1 – December 31
	Reporting Period: Annual Reports
	January 1 – December 31 *(the first report will cover December 31, 2005 through December 31, 2006)*

In addition, a "close-out" Annual Periodic Adverse Drug Experience Report, Special Pregnancy Report, and Program Evaluation Report will be submitted that covers the time period from the last report through December 30, 2005. Submit the Annual Periodic Adverse Drug Experience Report, the Psychiatric Quarterly Report, the Special Pregnancy Report, and the iPLEDGE Program Evaluation Report, including the "close-out" reports, to the Division of Dermatologic and Dental Drug Products and three copies of all the reports directly to:

Office of Drug Safety (HFD-400)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

FDA will re-evaluate the adequacy of the iPLEDGE program on a continuing basis regarding its success in achieving the goal of minimizing drug exposure during pregnancy and adherence to program components. Failure of iPLEDGE to achieve minimization of drug exposure during pregnancy, or failure to adhere to program components that may lead to pregnancy exposures, could lead to further regulatory action.

We agree that by November 12, 2005, Hoffman La-Roche will submit a Process Compliance Evaluation Plan designed to monitor, detect, and correct distribution outside the iPLEDGE program. FDA and Hoffman La-Roche have agreed that the Process Compliance Evaluation Plan will include the elements described in your submission of August 11, 2005, entitled "Agreements Needed for Compliance Evaluation Plan." The agreed upon plan will be implemented by January 1, 2006.

Pursuant to 21 CFR Part 208, FDA has determined that Accutane poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Accutane. FDA has determined that Accutane is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Accutane. In addition, patient labeling could help prevent serious adverse events related to use of the product.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted August 11, 2005 for the Package Insert, Patient Information/Informed Consents, and Medication Guide and for the blister card and carton labels. Marketing the product with FPL with text that is not identical to the approved text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 18-662/S-056.**" Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the labeling directly to:

Division of Drug Marketing, Advertising, and Communications (HFD-42)
Center for Drug Evaluation and Research
Food Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Florence Houn, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Florence Houn
8/12/05 09:21:15 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-056

APPROVED LABELING

ACCUTANE RISK MINIMIZATION ACTION PLAN: SUMMARY of iPLEDGE

iPLEDGE is a performance-linked access system that, for female patients of childbearing potential, ties pregnancy testing results and Accutane prescription and dispensing. The iPLEDGE program is a computer-based Risk Minimization Action Plan (RiskMAP) that involves registration of wholesalers and registration and activation of pharmacies, prescribers, and patients to control distribution, dispensing, prescribing, and access to Accutane.

I. Prescribing Program
   A. General requirements: Hoffman La-Roche will ensure that the following requirements are addressed by its RiskMAP, iPLEDGE:
      1. Accutane must only be distributed by iPLEDGE registered wholesalers, dispensed by iPLEDGE registered and activated pharmacies, prescribed by iPLEDGE registered and activated prescribers, and prescribed/dispensed for iPLEDGE registered and activated patients. Wholesalers, prescribers, pharmacies, and patients may voluntarily terminate registration or deactivate from the iPLEDGE program at any time. Hoffman La-Roche may remove from the iPLEDGE program registered wholesalers and activated pharmacies and activated prescribers if agreed upon responsibilities are not met.
      2. For females of childbearing potential, Accutane must only be prescribed initially on confirmation of two negative pregnancy tests (one screening test conducted when the decision is made to pursue qualification of the patient for Accutane and a second confirmation test conducted at a CLIA-certified laboratory within seven days of the office visit). Subsequent prescriptions are contingent on confirmation of a monthly negative pregnancy test conducted at a CLIA-certified laboratory.
   B. Wholesaler registration: Hoffman la-Roche will accept registrations for iPLEDGE from wholesalers who agree to the following:
      1. To register prior to distributing Accutane and re-register annually thereafter.
      2. To distribute only FDA-approved Accutane product.
      3. To only ship Accutane to wholesalers registered in the iPLEDGE program with prior written consent from Hoffman La-Roche or pharmacies licensed in the U.S. and registered and activated in the iPLEDGE program.
      4. To notify Hoffman La-Roche (or delegate) of any non-registered and/or non-activated pharmacy or unregistered wholesaler that attempts to order Accutane.
      5. To comply with inspection of wholesaler records for verification of compliance with the iPLEDGE program by Hoffman La-Roche (or delegate).
      6. To return to the Hoffman La-Roche (or delegate) any undistributed product if registration is revoked by Hoffman La-Roche or if the wholesaler chooses to not reregister annually.
      7. To provide product flow data to Hoffman La-Roche (or delegate) as detailed in the wholesalers agreement.
   C. Pharmacy registration and activation:
      1. Hoffman La-Roche will accept registration for and activate into iPLEDGE only pharmacies that, through the designated Responsible Site Pharmacist (RSP), agree to the following:
         a. To attest to knowing the risk and severity of fetal injury/birth defects from Accutane.
         b. To train all pharmacists, who participate in the filling and dispensing of Accutane prescriptions, on the iPLEDGE program requirements.

c. To comply with the iPLEDGE program requirements, and seek to ensure all pharmacists who participate in the filling and dispensing of Accutane prescriptions comply with the iPLEDGE program requirements.
d. To obtain Accutane product only from iPLEDGE registered wholesalers.
e. To not sell, borrow, loan, or otherwise transfer Accutane in any manner to or from another pharmacy.
f. To return to Hoffman La-Roche (or delegate) any unused product if registration is revoked by Hoffman La-Roche or if the pharmacy chooses to not reactivate annually.
g. To not fill Accutane for any party other than a qualified patient.
h. To dispense only FDA-approved Accutane products
i. To not dispense or otherwise obtain Accutane product through the internet or any other means outside of the iPLEDGE program.
j. To re-activate annually

2. Hoffman La-Roche will only accept registration for and activation into iPLEDGE, pharmacies whose pharmacists that will dispense Accutane, agree to the following:
   a. To be trained by the RSP concerning the iPLEDGE program requirements.
   b. To obtain authorization from the iPLEDGE program via the internet or telephone for every Accutane prescription.
   c. To write the risk Management Authorization (RMA) number on the prescription.
   d. To comply with iPLEDGE dispensing requirements.
      i Dispense in no more than a 30-day supply.
      ii Dispense with an Accutane Medication Guide
      iii Dispense only after authorization from the iPLEDGE program.
      iv Dispense prior to the "do not dispense to a patient after" date provided by the iPLEDGE system.
      v Dispense only with a new prescription for refills and another authorization from the iPLEDGE program.

D. Prescriber registration and activation:
   1. Hoffman La-Roche will accept registration for and activation into iPLEDGE only prescribers who agree to activate their registration, and reactivate annually thereafter by attesting to the following:
      a. To possess specified skills and knowledge
      b. To comply with iPLEDGE program requirements.
      c. To counsel female patients of childbearing potential before beginning Accutane therapy and on a monthly basis, to avoid pregnancy by using two forms of contraception simultaneously and continuously one month before, during, and one month after Accutane therapy, unless the patient commits to continuous abstinence.
      d. To not prescribe Accutane to any female patient of childbearing potential until verifying that she has a negative screening pregnancy test and monthly negative CLIA-certified pregnancy tests as well as at the completion of therapy and one month later.
      e. To report any pregnancy case that occurs while a female patient is on Accutane and for one month after the last dose to the pregnancy registry.
      f. To obtain the patient's signed informed consent prior to prescribing Accutane.
   2. Hoffman La-Roche will accept registration for and activation into iPLEDGE only prescribers who agree to access the iPLEDGE system via the internet or telephone to:
      a. Register each patient in the iPLEDGE program.
      b. Confirm monthly that each patient has received counseling and education.

c. For female patients of childbearing potential:
   i Enter the patient's two chosen forms of contraception each month.
   ii Enter monthly results from CLIA-certified laboratory conducted pregnancy test.
d. Ensure that all patients, and specifically female patients of childbearing potential, meet the requirements to be registered and activated in the iPLEDGE program.

The tasks of counseling patients, obtaining informed consent, and obtaining and inputting patient registration information, pregnancy test results, and reported adverse events (including pregnancy exposures) may be delegated to qualified staff.

E. Patient registration and activation: Hoffman La-Roche will accept registration for and activation into iPLEDGE only patients who meet the following conditions:
   1. Must be registered with the iPLEDGE program by the prescriber.
   2. Must understand that severe birth defects can occur with the use of Accutane by female patients.
   3. Must be reliable in understanding and carrying out instructions.
   4. Must sign a "Patient Information/Informed Consent (for all patients)" form that contains warnings about the potential risks associated with Accutane.
   5. Must fill the prescription within seven days of the office visit.
   6. Must donate blood while on Accutane and for one month after therapy has ended.
   7. Must not share Accutane with anyone.

   In addition to the requirements for all patients described above, female patients of childbearing potential must meet the following conditions:
   1. Must not be pregnant or breast-feeding.
   2. Must comply with the required pregnancy testing at a CLIA-certified laboratory.
   3. Must be capable of complying with the mandatory contraceptive measures for Accutane therapy, or commit to continuous abstinence from heterosexual intercourse, and understand behaviors associated with an increased risk of pregnancy.
   4. Must understand the responsibility to avoid pregnancy one month before, during, and one month after Accutane therapy.
   5. Must sign an additional "Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)" form, before starting Accutane therapy.
   6. Must access the iPLEDGE program via the internet or telephone before starting Accutane, on a monthly basis during therapy, and one month after the last dose to answer questions on the program requirements and to enter their two chosen forms of contraception.
   7. Must understand the purpose and importance of providing information to the iPLEDGE program should pregnancy occur while taking Accutane or within one month of the last dose.

II. Educational program: Hoffman La-Roche will implement an educational program for wholesalers, pharmacies, prescribers, and patients regarding the risks and benefits associated with the use of Accutane, education for contraception compliance, the requirements of the iPLEDGE program, and the requirements for interactions with the iPLEDGE program. Materials and proposals that address these educational requirements were submitted August 11, 2005 and include the following:
   A. Prescriber Educational Materials
      1. The iPLEDGE Program: Guide to Best Practices for Isotretinoin.
      2. Prescribing Checklist: First Office Visits for Females of Childbearing Potential.
      3. Prescribing Checklist: First Office Visits for Males and Females Who Cannot Get Pregnant.
      4. The iPLEDGE Program Contraception Referral Form and Contraception Counseling Guide.

5. The iPLEDGE Program: Prescriber Contraception Counseling Guide.
6. Recognizing Psychiatric disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin.

B. Pharmacy Educational Materials
1. The iPLEDGE Program: Pharmacist Guide for Isotretinoin

C. Patient Educational Materials
1. The iPledge Program: Patient Introductory Brochure
2. The iPLEDGE Program: Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant
3. The iPLEDGE Program: Guide to Isotretinoin for Female Patients Who Can Get Pregnant: The Importance of Avoiding Pregnancy on Isotretinoin
4. The iPLEDGE Program: Birth Control Workbook

D. Additional Information Sources:
1. iPLEDGE Information Internet Web Page
2. Call Center Support: A call center will be maintained to respond to healthcare practitioner, patient, pharmacist, and wholesaler questions and requests for information.

III. Reporting: Hoffman La-Roche will implement a reporting and collection system for: 1) serious adverse events associated with the use of Accutane that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) and 2) for sales and dispensing of drug outside the iPLEDGE program. Reports will include the following:

A. 15-Day Adverse Event Reports: In addition to the postmarketing adverse events that meet the requirements for reporting under 21 CFR 314.80(c), the following will be reported as 15-Day Adverse Drug Experience Report:
1. All pregnancy exposures.
2. All psychiatric adverse events including suicides, attempted suicides, and suicidal ideation.

B. Periodic Adverse Drug Experience Reports
1. Narrative summary and analysis of information in the report.
2. Analysis by system organ class of the 15-Day Adverse Event Reports submitted in the preceding year.
3. Reports of adverse events not previously submitted as 15-Day Adverse Event Reports.
4. A history of action taken due to the occurrence of adverse events since the previous Periodic Adverse Drug Experience Report.

C. Psychiatric Quarterly Report: All psychiatric adverse events associated with the use of isotretinoin will be submitted quarterly as a supplementary report to the Periodic Adverse Drug Experience Report.

D. Special Pregnancy Quarterly Report: The following data will be submitted as a supplementary report to the Periodic Adverse Drug Experience Report.
a. All pregnancy exposures to Accutane in the U.S.
b. All cases of fetal malformation resulting from pregnancy exposure to Accutane in the U.S.
c. Copies of all 15-Day Adverse Event Reports for cases of pregnancy exposure to Accutane in the U.S. and fetal malformation resulting from Accutane exposure in the U.S.

E. Non-Compliant Distribution Reports: A description of all instances of sales and dispensing of Accutane product outside of the iPLEDGE program will be submitted within 15 days of Hoffman La-Roche's receipt of new information. Reports will include the following:

1. Information on the sale of any Accutane product by a wholesaler to an unregistered and/or un-activated pharmacy or unregistered wholesaler.
2. Information on dispensing of any Accutane product by an unregistered and/or un-activated pharmacy.
3. The details of the information to be submitted and the content, format, and frequency of the report will be agreed to by FDA.

IV. iPLEDGE Program Evaluation: Hoffman La-Roche, or their delegate, will conduct an evaluation of the effectiveness of the iPLEDGE program in minimizing drug exposure during pregnancy. The evaluation program will include the following:

A. Pregnancy Registry: Hoffman La-Roche will establish a pregnancy registry to actively collect information on any pregnancies occurring in female patients treated with Accutane. Paternal (exposed and non-exposed) cases will be excluded from the registry. The content, format, and frequency of reporting will be agreed to by FDA. The registry will be designed to incorporate the following:

1. Objectives
   a. Determine Accutane exposure status for each reported pregnancy.
   b. Document the outcome of each Accutane exposed pregnancy.
   c. Provide pregnancy documentation to assist in the evaluation, by root cause analysis, of iPLEDGE failures of each exposed pregnancy.
   d. Provide pregnancy data in periodic reports to FDA.
2. Outcome measures
   a. Pregnancy outcome.
   b. Congenital anomalies (major and minor birth defects).
   c. Other pregnancy or delivery complications or abnormalities.
   d. Neonate/infant outcomes.
   e. Infant follow-up for reports of fetal exposure.
3. Failure Mode and Effects Analysis Plan
   a. Hoffman La-Roche, or its delegate, will analyze the incidences of pregnancy in women exposed to Accutane. Analyses will include patient (monthly) assessments of the following:
      i Patient interaction with iPLEDGE to determine patient knowledge, attitudes, and behavior regarding iPLEDGE requirements.
      ii Patient acknowledgement of receipt of educational materials and contraceptive counseling.
   b. Hoffman La-Roche, or its delegate, will analyze the root cause for program failure for patients who become pregnant, including
      i Determination of patient knowledge, attitudes, and behavior regarding iPLEDGE requirements.
      ii Determination of the most likely cause of pregnancy.

B. iPLEDGE Process Compliance Evaluation Plan:
Hoffman La-Roche will submit a Process Compliance Evaluation Plan by November 12, 2005 designed to monitor, detect, and correct distribution outside the iPLEDGE program. FDA and Hoffman La-Roche have agreed that the Process Compliance Evaluation Plan will include the following elements as described in the submission dated August 11, 2005, entitled "Agreements Needed for Compliance Evaluation Plan." The agreed upon plan will be implemented by January 1, 2006.

1. Wholesaler Compliance: Hoffman La-Roche will:

a. Implement an evaluation plan, as agreed upon with FDA, to assess wholesaler compliance with the requirements of the iPLEDGE program and report on the data collected in a manner and at the frequency agreed upon with FDA.
b. Implement a corrective action plan, as agreed upon with FDA, to address wholesaler noncompliance with the iPLEDGE program.

2. Pharmacy Compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan, as agreed upon with FDA, to assess pharmacy compliance with the requirements of the iPLEDGE program and report on the data collected in a manner and at the frequency agreed upon with FDA.
   b. Implement a corrective action plan, as agreed upon with FDA, to address noncompliance with the iPLEDGE program.
3. Prescriber Compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan, as agreed upon with FDA, to assess prescriber compliance with the requirements of the iPLEDGE program and report on the data collected at the frequency agreed upon with FDA.
   b. Implement a corrective action plan to address prescriber noncompliance with iPLEDGE requirements.
4. Patient compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan to assess patient compliance with iPLEDGE program requirements.
      i Independent Validation of iPLEDGE Patient Compliance: Hoffman La-Roche, or its delegate, will develop an independent means to audit patient compliance with the requirements of the iPLEDGE program and to report on the data collected at the frequency agreed upon with FDA.
      ii Evaluation of patients lost to follow-up or who discontinued Accutane: Hoffman La-Roche, or its delegate, will develop a method to allow evaluation of patients lost to follow-up or who discontinued Accutane to assess the reason(s) for no longer being in iPLEDGE.
   b. Implement a corrective action plan to address patient noncompliance with iPLEDGE.

Roche

ACCUTANE®

(isotretinoin capsules)

R_x only

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

Accutane must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects which have been documented following Accutane exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

If pregnancy does occur during treatment of a female patient who is taking Accutane, Accutane must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Special Prescribing Requirements

Because of Accutane's teratogenicity and to minimize fetal exposure, Accutane is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE™. Accutane must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**).

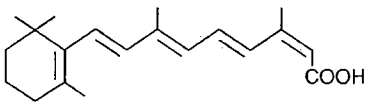
Table 1 Monthly Required iPLEDGE Interactions

	Female Patients Of Childbearing Potential	Male Patients, And Female Patients Not Of Childbearing Potential
PRESCRIBER		
Confirms patient counseling	X	X
Enters the 2 contraception methods chosen by the patient	X	
Enters pregnancy test results	X	
PATIENT		
Answers educational questions before every prescription	X	
Enters 2 forms of contraception	X	
PHARMACIST		
Calls system to get an authorization	X	X

DESCRIPTION

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

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



CLINICAL PHARMACOLOGY

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

Nodular Acne

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

Pharmacokinetics

Absorption

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

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

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

*Eating a standardized high-fat meal

Distribution

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

Metabolism

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

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

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

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

Elimination

Following oral administration of an 80 mg dose of ^{14}C-isotretinoin as a liquid suspension, ^{14}C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg oral dose of Accutane to 74 healthy adult subjects under fed conditions, the mean ± SD elimination half-lives ($t_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin were 21.0 ± 8.2 hours and 24.0 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43 in patients with cystic acne.

Special Patient Populations

Pediatric Patients

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

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

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

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

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

INDICATIONS AND USAGE

Severe Recalcitrant Nodular Acne

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

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

CONTRAINDICATIONS

Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND WARNINGS.

Allergic Reactions

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

WARNINGS

Psychiatric Disorders

Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin.* Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Accutane therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. Signs and symptoms of depression, as described in the brochure ("Recognizing Psychiatric Disorders in Adolescents and Young Adults"), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop Accutane and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. 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 Accutane therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Accutane therapy.

Pseudotumor Cerebri

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

Pancreatitis

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

Lipids

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with Accutane. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving Accutane in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the

effects on triglycerides, HDL, and cholesterol were reversible upon cessation of Accutane therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane.[5]

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

The cardiovascular consequences of hypertriglyceridemia associated with Accutane are unknown. *Animal Studies*: In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

Hearing Impairment

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

Hepatotoxicity

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

Inflammatory Bowel Disease

Accutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Accutane treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see **ADVERSE REACTIONS: Gastrointestinal**).

Skeletal

Bone Mineral Density

Effects of multiple courses of Accutane on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label

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

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

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

Hyperostosis

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

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

Premature Epiphyseal Closure

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

Vision Impairment

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

Corneal Opacities

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

Decreased Night Vision

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

PRECAUTIONS

Accutane must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE. Registered and activated pharmacies must receive Accutane only from wholesalers registered with iPLEDGE.

iPLEDGE program requirements for wholesalers, prescribers, and pharmacists are described below:

Wholesalers:

For the purpose of the iPLEDGE program, the term wholesaler refers to wholesaler, distributor, and/or chain pharmacy distributor. To distribute Accutane, wholesalers must be registered with iPLEDGE, and agree to meet all iPLEDGE requirements for wholesale distribution of isotretinoin products. Wholesalers must register with iPLEDGE by signing and returning the iPLEDGE wholesaler agreement that affirms they will comply with all iPLEDGE requirements for distribution of isotretinoin. These include:

- Registering prior to distributing isotretinoin and reregistering annually thereafter
- Distributing only FDA approved isotretinoin product
- Only shipping isotretinoin to
  - wholesalers registered in the iPLEDGE program with prior written consent from the manufacturer or
  - pharmacies licensed in the US and registered and activated in the iPLEDGE program
- Notifying the isotretinoin manufacturer (or delegate) of any non-registered and/or non-activated pharmacy or unregistered wholesaler that attempts to order isotretinoin
- Complying with inspection of wholesaler records for verification of compliance with the iPLEDGE program by the isotretinoin manufacturer (or delegate)
- Returning to the manufacturer (or delegate) any undistributed product if registration is revoked by the manufacturer or if the wholesaler chooses to not reregister annually
- Providing product flow data to manufacturer (or delegate) as detailed in the wholesalers agreement

Prescribers:

To prescribe isotretinoin, the prescriber must be registered and activated with the pregnancy risk management program iPLEDGE. Prescribers can register by signing and returning the completed registration form. Prescribers can only activate their registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know how to diagnose and treat the various presentations of acne.
- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.
- I have the expertise to provide the patient with detailed pregnancy prevention counseling or I will refer her to an expert for such counseling, reimbursed by the manufacturer.
- I will comply with the iPLEDGE program requirements described in the booklets entitled *The iPLEDGE Program Guide to Best Practices for Isotretinoin* and *The iPLEDGE Program Prescriber Contraception Counseling Guide.*
- Before beginning treatment of female patients of child bearing potential with isotretinoin and on a monthly basis, the patient will be counseled to avoid pregnancy by using two forms of contraception simultaneously and continuously one month before, during, and one month after isotretinoin therapy, unless the patient commits to continuous abstinence.
- I will not prescribe isotretinoin to any female patient of childbearing potential until verifying she has a negative screening pregnancy test and monthly negative CLIA-certified (Clinical Laboratory Improvement Amendment) pregnancy tests. Patients should have a pregnancy test at the completion of the entire course of isotretinoin and another pregnancy test 1 month later.
- I will report any pregnancy case that I become aware of while the female patient is on isotretinoin or 1 month after the last dose to the pregnancy registry.

To prescribe isotretinoin, the Prescriber must access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) to:

1) Register each patient in the iPLEDGE program.
2) Confirm monthly that each patient has received counseling and education.
3) For *female patients of childbearing potential*:
    - Enter patient's two chosen forms of contraception each month.
    - Enter monthly result from CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be prescribed to female patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be dispensed by a pharmacy registered and activated with the pregnancy risk management program iPLEDGE and only when the registered patient meets all the requirements of the

iPLEDGE program. Meeting the requirements for a female patient of childbearing potential signifies that she:

- Has been counseled and has signed a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin. The patient must sign the informed consent form before starting treatment and patient counseling must also be done at that time and on a monthly basis thereafter.

- Has had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient forisotretinoin. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the 2 tests should be at least 19 days.

  - For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period and within 7 days of the office visit, immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.

  - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done within 7 days following the office visit, immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.

- Has had a negative result from a urine or serum pregnancy test in a CLIA- certified laboratory before receiving each subsequent course of isotretinoin. A pregnancy test must be repeated every month, in a CLIA-certified laboratory, prior to the female patient receiving each prescription.

- Has selected and has committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence from heterosexual contact, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of isotretinoin therapy, during isotretinoin therapy, and for 1 month after discontinuing isotretinoin therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

  If the patient has unprotected heterosexual intercourse at any time 1 month before, during, or 1 month after therapy, she must:

  1. Stop taking Accutane immediately, if on therapy
  2. Have a pregnancy test at least 19 days after the last act of unprotected heterosexual intercourse
  3. Start using 2 forms of effective contraception simultaneously again for 1 month before resuming Accutane therapy
  4. Have a second pregnancy test after using 2 forms of effective contraception for 1 month as described above depending on whether she has regular menses or not.

Effective forms of contraception include both primary and secondary forms of contraception:

Primary forms	Secondary forms
• tubal sterilization • partner's vasectomy • intrauterine device • hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)	*Barrier forms (always used with spermicide):* • male latex condom • diaphragm • cervical cap *Others:* • vaginal sponge (contains spermicide)

Any birth control method can fail. There have been reports of pregnancy from female patients who have used oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products; these pregnancies occurred while these patients were taking Accutane. These reports are more frequent for female patients who use only a single method of contraception. Therefore, it is critically important that female patients of childbearing potential use 2 effective forms of contraception simultaneously. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

Using two forms of contraception simultaneously substantially reduces the chances that a female will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane (see **PRECAUTIONS: Drug Interactions**). Although hormonal contraceptives are highly effective, 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.

If a pregnancy does occur during isotretinoin treatment, isotretinoin must be discontinued immediately. The patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or 1 month after isotretinoin therapy must be reported immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

All Patients

Isotretinoin is contraindicated in female patients who are pregnant. To receive isotretinoin all patients must meet all of the following conditions:

- Must be registered with the iPLEDGE program by the prescriber
- Must understand that severe birth defects can occur with the use of isotretinoin by female patients
- Must be reliable in understanding and carrying out instructions
- Must sign a Patient Information/Informed Consent (for all patients) form that contains warnings about the potential risks associated with isotretinoin
- Must fill the prescription within 7 days of the office visit
- Must not donate blood while on isotretinoin and for 1 month after treatment has ended
- Must not share isotretinoin with anyone, even someone who has similar symptoms

Female Patients of Childbearing Potential

Isotretinoin is contraindicated in female patients who are pregnant. In addition to the requirements for all patients described above, female patients of childbearing potential must meet the following conditions:

- Must NOT be pregnant or breast-feeding
- Must comply with the required pregnancy testing at a CLIA-certified laboratory
- Must be capable of complying with the mandatory contraceptive measures required for isotretinoin therapy, or commit to continuous abstinence from heterosexual intercourse, and understand behaviors associated with an increased risk of pregnancy
- Must understand that it is her responsibility to avoid pregnancy one month before, during and one month after isotretinoin therapy
- Must have signed an additional Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form, before starting isotretinoin, that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin
- Must access the iPLEDGE program via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654), before starting isotretinoin, on a monthly basis during therapy, and 1 month after the last dose to answer questions on the program requirements and to enter the patient's two chosen forms of contraception
- Must have been informed of the purpose and importance of providing information to the iPLEDGE program should she become pregnant while taking isotretinoin or within 1 month of the last dose

Pharmacists:

To dispense isotretinoin, pharmacies must be registered and activated with the pregnancy risk management program iPLEDGE.

The Responsible Site Pharmacist must register the pharmacy by signing and returning the completed registration form. After registration, the Responsible Site Pharmacist can only activate the pharmacy registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I will train all pharmacists, who participate in the filling and dispensing of isotretinoin prescription, on the iPLEDGE program requirements.
- I will comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE program requirements described in the booklet entitled *The iPLEDGE Program Pharmacist Guide for Isotretinoin.*
- I will obtain Accutane product only from iPLEDGE registered wholesalers.
- I will not sell, buy, borrow, loan or otherwise transfer isotretinoin in any manner to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if registration is revoked by the manufacturer or if the pharmacy chooses to not reactivate annually.
- I will not fill isotretinoin for any party other than a qualified patient.

To dispense isotretinoin, the pharmacist must:

1) be trained by the Responsible Site Pharmacist concerning the iPLEDGE program requirements.

2) obtain authorization from the iPLEDGE program via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) for every isotretinoin prescription. Authorization signifies that the patient has met all program requirements and is qualified to receive isotretinoin.

3) write the Risk Management Authorization (RMA) number on the prescription.

Accutane must only be dispensed:

- in no more than a 30-day supply
- with an Accutane Medication Guide
- after authorization from the iPLEDGE program
- prior to the "do not dispense to patient after" date provided by the iPLEDGE system (within 7 days of the office visit)
- with a new prescription for refills and another authorization from the iPLEDGE program (No automatic refills are allowed)

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

Accutane must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE program. Only FDA-approved Accutane products must be distributed, prescribed, dispensed, and used. Patients must fill Accutane prescriptions only at US licensed pharmacies.

A description of the iPLEDGE program educational materials available with iPLEDGE is provided below. The main goal of these educational materials is to explain the iPLEDGE program requirements and to reinforce the educational messages.

1) *The iPLEDGE Program Guide to Best Practices for Isotretinoin* includes: isotretinoin teratogenic potential, information on pregnancy testing, and the method to complete a qualified isotretinoin prescription.

2) *The iPLEDGE Program Prescriber Contraception Counseling Guide* includes: specific information about effective contraception, the limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure and pregnancy and the methods to evaluate pregnancy risk.

3) *The iPLEDGE Program Pharmacist Guide for Isotretinoin* includes: isotretinoin teratogenic potential and the method to obtain authorization to dispense an isotretinoin prescription.

4) The iPLEDGE program is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The iPLEDGE program includes information on the risks and benefits of isotretinoin which is linked to the Medication Guide dispensed by pharmacists with each isotretinoin prescription.

5) Female patients not of childbearing potential and male patients, and female patients of childbearing potential are provided with separate booklets. Each booklet contains information on isotretinoin therapy including precautions and warnings, a Patient Information/Informed Consent (for all patients) form, and a toll-free line which provides isotretinoin information in 2 languages.

6) The booklet for female patients not of childbearing potential and male patients, *The iPLEDGE Program Guide to Isotretinoin for Male Patients & Female Patients Who Cannot Get Pregnant*, also includes information about male reproduction and a warning not to share isotretinoin with others or to donate blood during isotretinoin therapy and for 1 month following discontinuation of isotretinoin.

7) The booklet for female patients of childbearing potential, *The iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant*, includes a referral program that offers female patients free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; and a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form concerning birth defects.

8) The booklet, *The iPLEDGE Program Birth Control Workbook* includes information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, the rates of possible contraceptive failure and a toll-free contraception counseling line.

9) In addition, there is a patient educational DVD with the following videos — "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin" (see **Information for Patients**).

General

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

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

Information for Patients

See **PRECAUTIONS** and **Boxed CONTRAINDICATIONS AND WARNINGS.**

- Patients must be instructed to read the Medication Guide supplied as required by law when Accutane is dispensed. The complete text of the Medication Guide is reprinted at the end of this document. For additional information, patients must also be instructed to read the iPLEDGE program patient educational materials. All patients must sign the Patient Information/Informed Consent (for all patients) form.

- Female patients of childbearing potential must be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use 2 forms of effective contraception simultaneously for 1 month before starting Accutane, while taking Accutane, and for 1 month after Accutane has been stopped, unless they commit to continuous abstinence from heterosexual intercourse. They should also sign a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form prior to beginning Accutane therapy. They should be given an opportunity to view the patient DVD provided by the manufacturer to the prescriber. The DVD 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 and comprehensive information about types of potential birth defects which could occur if a female patients who is pregnant takes Accutane at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test, in a CLIA-certified laboratory, performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see **Boxed CONTRAINDICATIONS AND WARNINGS** and **PRECAUTIONS**).

- Accutane is found in the semen of male patients taking Accutane, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses; however 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.

- Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Accutane treatment, patients and family members should be asked about any history of psychiatric disorder, and at each visit during

treatment patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. **Signs and symptoms of depression include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment.** Patients should stop Accutane and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Accutane treatment may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. 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 Accutane therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Accutane therapy.

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

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

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

- Patients should be reminded to take Accutane with a meal (see **DOSAGE AND ADMINISTRATION**). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.

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

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

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

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

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

- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane. Consideration should be given to discontinuation of Accutane if any significant abnormality is found.

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

Hypersensitivity

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

Drug Interactions

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

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

- *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from female patients who have used combined oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products. These reports are more frequent for female patients who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important for female patients 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 (see **PRECAUTIONS**).

- *Norethindrone/ethinyl estradiol:* In a study of 31 premenopausal female patients with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent,

Accutane at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). 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.

- *St. John's Wort:* **Accutane use is associated with depression in some patients (see WARNINGS: Psychiatric Disorders and ADVERSE REACTIONS: Psychiatric).** Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

- *Phenytoin:* Accutane has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane. Therefore, caution should be exercised when using these drugs together.

- *Systemic Corticosteroids:* Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane. Therefore, caution should be exercised when using these drugs together.

Laboratory Tests

Pregnancy Test

- Female patients of childbearing potential must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests must be at least 19 days.

- For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period and within 7 days following the office visit, immediately preceding the beginning of Accutane therapy and after the patient has used 2 forms of contraception for 1 month.

- For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done within 7 days following the office visit, immediately preceding the beginning of Accutane therapy and after the patient has used 2 forms of contraception for 1 month.

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

- *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see **WARNINGS: Lipids**).

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

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

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

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day,

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

Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND WARNINGS.

Nursing Mothers

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

Pediatric Use

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

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

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

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

Geriatric Use

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

ADVERSE REACTIONS

Clinical Trials and Postmarketing Surveillance

The adverse reactions listed below reflect the experience from investigational studies of Accutane, and the postmarketing experience. The relationship of some of these events to Accutane therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Accutane are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal passage, and eyes).

Dose Relationship

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

Body as a Whole

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

Cardiovascular

palpitation, tachycardia, vascular thrombotic disease, stroke

Endocrine/Metabolic

hypertriglyceridemia (see **WARNINGS: Lipids**), alterations in blood sugar levels (see **PRECAUTIONS: Laboratory Tests**)

Gastrointestinal

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

Hematologic

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

Musculoskeletal

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

Neurological

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

Psychiatric

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

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

Reproductive System

abnormal menses

Respiratory

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

Skin and Appendages

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

Special Senses

Hearing

hearing impairment (see **WARNINGS: Hearing Impairment**), tinnitus.

Vision

corneal opacities (see **WARNINGS: Corneal Opacities**), decreased night vision which may persist (see **WARNINGS: Decreased Night Vision**), cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

Urinary System

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

Laboratory

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

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

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

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

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

OVERDOSAGE

The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice (>600 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the rat dose for total body surface area and >300 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve without apparent residual effects.

Accutane causes serious birth defects at any dosage (see **Boxed CONTRAINDICATIONS AND WARNINGS**). Female patients of childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the boxed CONTRAINDICATIONS AND WARNINGS. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in **PRECAUTIONS**. Educational materials for such patients can be obtained by calling the manufacturer. Because an overdose would be expected to result in higher levels of isotretinoin in semen than found during a normal treatment course, male patients should use a condom, or avoid reproductive sexual activity with a female patient who is or might become pregnant, for 1 month after the overdose. All patients with isotretinoin overdose should not donate blood for at least 1 month.

DOSAGE AND ADMINISTRATION

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

The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related. Adult patients whose disease

is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

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

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of Accutane, even in low doses, has not been studied, and is not recommended. It is important that Accutane be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Accutane on bone loss is unknown (see **WARNINGS: Skeletal: Bone Mineral Density**, **Hyperostosis**, and **Premature Epiphyseal Closure**).

Contraceptive measures must be followed for any subsequent course of therapy (see **PRECAUTIONS**).

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

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

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

INFORMATION FOR PHARMACISTS

Access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) to obtain an authorization and the **"do not dispense to patient after" date.** Accutane must only be dispensed in no more than a 30-day supply.

REFILLS REQUIRE A NEW PRESCRIPTION AND A NEW AUTHORIZATION FROM THE iPLEDGE SYSTEM.

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

HOW SUPPLIED

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

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

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

Storage

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

REFERENCES

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

Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)

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

Read each item below and initial in the space provided to show that you understand each item and agree to follow your doctor's instructions. **Do not sign this consent and do not take isotretinoin if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and initial each item before signing the consent.

_____
(Patient's Name)

1. I understand that there is a very high chance that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking isotretinoin. This can happen with any amount and even if taken for short periods of time. This is why I must not be pregnant while taking isotretinoin.

   Initial: _____

2. I understand that I must not get pregnant 1 month before, during the entire time of my treatment, and for 1 month after the end of my treatment with isotretinoin.

Initial: _____

3. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) **at the same time**. The only exceptions are if I have had surgery to remove the uterus (a hysterectomy) or both of my ovaries (bilateral oophorectomy), or my doctor has medically confirmed that I am post-menopausal.

   Initial: _____

4. I understand that hormonal birth control products are among the most effective forms of birth control. Combination birth control pills and other hormonal products include skin patches, shots, under-the-skin implants, vaginal rings, and intrauterine devices (IUDs). Any form of birth control can fail. That is why I must use 2 different birth control methods starting 1 month before, during, and for 1 month after stopping therapy at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is hormonal birth control.

   Initial: _____

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

Primary forms	Secondary forms
• tying my tubes (tubal sterilization) • partner's vasectomy • intrauterine device • hormonal (combination birth control pills, skin patches, shots, under-the-skin implants, or vaginal ring)	*Barrier forms (always used with spermicide):* • male latex condom • diaphragm • cervical cap *Others:* • vaginal sponge (contains spermicide)

   A diaphragm, condom, and cervical cap must each be used with spermicide, a special cream that kills sperm

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

   Initial: _____

6. I will talk with my doctor about any medicines including herbal products I plan to take during my isotretinoin treatment because hormonal birth control methods may not work if I am taking certain medicines or herbal products.

   Initial: _____

7. I may receive a free birth control counseling session from a doctor or other family planning expert. My isotretinoin doctor can give me an isotretinoin Patient Referral Form for this free consultation.

Initial: _____

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

   Initial: _____

9. I can not get my first prescription for isotretinoin unless my doctor has told that I have 2 negative pregnancy test results. The first pregnancy test should be done when my doctor decides to prescribe isotretinoin. The second pregnancy test must be done in a lab during the first 5 days of my menstrual period right before starting isotretinoin therapy treatment, or as instructed by my doctor. I will then have 1 pregnancy test; in a lab.

   - every month during treatment.
   - at the end of treatment
   - and 1 month after stopping treatment

   I must not start taking isotretinoin until I am sure that I am not pregnant, have negative results from 2 pregnancy tests, and the second test has been done in a lab.

   Initial: _____

10. I have read and understand the materials my doctor has given to me, including *The iPLEDGE Program Guide for Isotretinoin for Female Patients Who Can Get Pregnant, The iPLEDGE Birth Control Workbook* and *The iPLEDGE Program Patient Introductory Brochure.* .

    My doctor gave me and asked me to watch the DVD containing a video about birth control and a video about birth defects and isotretinoin.

    I was told about a private counseling line that I may call for more information about birth control. I have received information on emergency birth control.

    Initial: _____

11. I must stop taking isotretinoin right away and call my doctor if I get pregnant, miss my expected menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods at any time.

    Initial: _____

12. My doctor gave me information about the purpose and importance of providing information to the iPLEDGE program should I become pregnant while taking isotretinoin or within 1 month of the last dose. If I become pregnant, I agree to be contacted by the iPLEDGE program and be asked questions about my pregnancy. I also understand that if I become pregnant, information about my pregnancy, my health, and my baby's health may be given to the maker of isotretinoin and government health regulatory authorities.

    Initial: _____

13. I understand that being qualified to receive isotretinoin in the iPLEDGE program means that I:

- have had 2 negative urine or blood pregnancy tests before receiving the first isotretinoin prescription. The second test must be done in a lab. I must have a negative result from a urine or blood pregnancy test done in a lab repeated each month before I receive another isotretinoin prescription.

- have chosen and agreed to use 2 forms of effective birth control at the same time. At least 1 method must be a primary form of birth control, **unless I have chosen never to have sexual contact with a male (abstinence)**, or I have undergone a hysterectomy. I must use 2 forms of birth control for at least 1 month before I start isotretinoin therapy, during therapy, and for 1 month after stopping therapy. I must receive counseling, repeated on a monthly basis, about birth control and behaviors associated with an increased risk of pregnancy.

- have signed a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) that contains warnings about the chance of possible birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.

- have been informed of and understand the purpose and importance of providing information to the iPLEDGE program should I become pregnant while taking isotretinoin or within 1 month of the last dose. I agree to be contacted by the iPLEDGE program and be asked questions about my pregnancy.

- have interacted with the iPLEDGE program before starting isotretinoin and on a monthly basis to answer questions on the program requirements and to enter my two chosen forms of birth control.

Initial: _____

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

Initial: _____

I now authorize my doctor _____ to begin my treatment with isotretinoin.

Patient Signature:_____ Date: _____

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

Please print: Patient Name and Address_____

_____ Telephone _____

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

Doctor Signature: _____ Date: _____

**PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S MEDICAL RECORD.
PLEASE PROVIDE A COPY TO THE PATIENT.**

Patient Information/Informed Consent (for all patients):

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

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

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

1. I, _____,
   (Patient's Name)
   understand that isotretinoin 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 doctor has told me about my choices for treating my acne.

   Initials: _____

3. I understand that there are serious side effects that may happen while I am taking isotretinoin. These have been explained to me. These side effects include serious birth defects in babies of pregnant patients. (Note: There is a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)

   Initials: _____

4. I understand that some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental problems. Symptoms of depression include sad, "anxious" or empty mood, irritability, acting on dangerous impulses, 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 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 becoming aggressive or violent. No one knows if isotretinoin caused these behaviors or if they would have happened even if the person did not take isotretinoin. Some people have had other signs of depression while taking isotretinoin (see #7 below).

   Initials: _____

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

Initials: _____

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

   Initials: _____

7. Once I start taking isotretinoin, I agree to stop using isotretinoin and tell my doctor right away if any of the following signs and symptoms of depression or psychosis happen. I:
   - Start to feel sad or have crying spells
   - Lose interest in activities I once enjoyed
   - Sleep too much or have trouble sleeping
   - Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
   - Have a change in my appetite or body weight
   - Have trouble concentrating
   - Withdraw from my friends or family
   - Feel like I have no energy
   - Have feelings of worthlessness or guilt
   - Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
   - Start acting on dangerous impulses
   - Start seeing or hearing things that are not real

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

    Initials: _____

11. I have read *The iPLEDGE Program Patient Introductory Brochure,* and other materials my provider gave me containing important safety information about isotretinoin. I understand all the information I received.

    Initials: _____

12. My doctor and I have decided I should take isotretinoin. I understand that I must be qualified in the iPLEDGE program to have my prescription filled each month. I understand that I can stop taking isotretinoin at any time. I agree to tell my doctor if I stop taking isotretinoin.

    Initials: _____

I now allow my doctor _____ to begin my treatment with isotretinoin.

Patient Signature: _____ Date: _____

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

Patient Name (print) _____

Patient Address _____ Telephone (___.___.___)

_____

I have:

- fully explained to the patient, _____, the nature and purpose of isotretinoin treatment, including its benefits and risks
- given the patient the appropriate educational materials, *The iPLEDGE Program Patient Introductory Brochure* and asked the patient if he/she has any questions regarding his/her treatment with isotretinoin
- answered those questions to the best of my ability

Doctor Signature: _____ Date: _____

PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S MEDICAL RECORD. PLEASE PROVIDE A COPY TO THE PATIENT.

MEDICATION GUIDE

ACCUTANE (ACK-U-TANE)

(isotretinoin capsules)

Read the Medication Guide that comes with Accutane before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

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

- Accutane is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics.
- Because Accutane can cause birth defects, Accutane is only for patients who can understand and agree to carry out all of the instructions in the iPLEDGE program.
- Accutane may cause serious mental health problems.

1. **Birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births.** Female patients who are pregnant or who plan to become pregnant must not take Accutane. **Female patients must not get pregnant:**

   - for 1 month before starting Accutane
   - while taking Accutane
   - for 1 month after stopping Accutane.

   If you get pregnant while taking Accutane, stop taking it right away and call your doctor. Doctors and patients should report all cases of pregnancy to:

   - FDA MedWatch at 1-800-FDA-1088, and
   - the iPLEDGE pregnancy registry at 1-800-495-0654

2. **Serious mental health problems.** Accutane may cause:
   - **depression**
   - **psychosis** (seeing or hearing things that are not real)
   - **suicide**. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives.

   Stop Accutane and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

   - 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 guilt
   - start having thoughts about hurting yourself or taking your own life (suicidal thoughts)
   - start acting on dangerous impulses
   - start seeing or hearing things that are not real

After stopping Accutane, you may also need follow-up mental health care if you had any of these symptoms.

What is Accutane?

Accutane is a medicine taken by mouth to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. Accutane can cause serious side effects (see **"What is the most important information I should know about Accutane?"**). Accutane can only be:

- prescribed by doctors that are registered in the iPLEDGE program

- dispensed by a pharmacy that is registered with the iPLEDGE program
- given to patients who are registered in the iPLEDGE program and agree to do everything required in the program

What is severe nodular acne?

Severe nodular acne is when 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.

Who should not take Accutane?

- **Do not take Accutane if you are pregnant, plan to become pregnant, or become pregnant during Accutane treatment.** Accutane causes severe birth defects. See **"What is the most important information I should know about Accutane?"**

- **Do not take Accutane if you are allergic to anything in it.** Accutane contains **parabens** as the preservative. See the end of this Medication Guide for a complete list of ingredients in Accutane.

What should I tell my doctor before taking Accutane?

Tell your doctor if you or a family member has any of the following health conditions:

- mental problems
- asthma
- liver disease
- diabetes
- heart disease
- bone loss (osteoporosis) or weak bones
- an eating problem called anorexia nervosa (where people eat too little),
- food or medicine allergies

Tell your doctor if you are pregnant or breastfeeding. Accutane must not be used by women who are pregnant or breastfeeding.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Accutane and certain other medicines can interact with each other, sometimes causing serious side effects. Especially tell your doctor if you take:

- **Vitamin A supplements.** Vitamin A in high doses has many of the same side effects as Accutane. Taking both together may increase your chance of getting side effects.
- **Tetracycline antibiotics.** Tetracycline antibiotics taken with Accutane can increase the chances of getting increased pressure in the brain.
- **Progestin-only birth control pills (mini-pills).** They may not work while you take Accutane. Ask your doctor or pharmacist if you are not sure what type you are using.
- **Dilantin (phenytoin).** This medicine taken with Accutane may weaken your bones.
- **Corticosteroid medicines.** These medicines taken with Accutane may weaken your bones.
- **St. John's Wort.** This herbal supplement may make birth control pills work less effectively.

These medicines should not be used with Accutane unless your doctor tells you it is okay.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take any new medicine without talking with your doctor.

How should I take Accutane?

- You must take Accutane exactly as prescribed. You must also follow all the instructions of the iPLEDGE program. Before prescribing Accutane, your doctor will:
  - explain the iPLEDGE program to you
  - have you sign the Patient Information/Informed Consent (for all patients). Female patients who can get pregnant must also sign another consent form.

  You will not be prescribed Accutane if you can not agree to or follow all the instructions of the iPLEDGE program.

- You will get no more than a 30-day supply of Accutane at a time. This is to make sure you are following the Accutane iPLEDGE program. You should talk with your doctor each month about side effects.

- The amount of Accutane you take has been specially chosen for you. It is based on your body weight, and may change during treatment.

- Take Accutane 2 times a day with a meal, unless your doctor tells you otherwise. **Swallow your Accutane capsules whole with a full glass of liquid. Do not chew or suck on the capsule.** Accutane can hurt the tube that connects your mouth to your stomach (esophagus) if it is not swallowed whole.

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

- If you take too much Accutane or overdose, call your doctor or poison control center right away.

- Your acne may get worse when you first start taking Accutane. This should last only a short while. Talk with your doctor if this is a problem for you.

- You must return to your doctor as directed to make sure you don't have signs of serious side effects. Your doctor may do blood tests to check for serious side effects from Accutane. Female patients who can get pregnant will get a pregnancy test each month.

- Female patients who can become pregnant must agree to use 2 separate forms of effective birth control at the same time 1 month before, while taking, and for 1 month after taking Accutane. **You must access the iPLEDGE system to answer questions about the program requirements and to enter your 2 chosen forms of birth control.** To access the iPLEDGE system, go to www.ipledgeprogram.com or call 1-866-495-0654.

  You must talk about effective birth control methods with your doctor or go for a free visit to talk about birth control with another doctor or family planning expert. Your doctor can arrange this free visit, which will be paid for by the company that makes Accutane.

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

What should I avoid while taking Accutane?

- **Do not get pregnant** while taking Accutane and for 1 month after stopping Accutane. See **"What is the most important information I should know about Accutane?"**

- **Do not breast feed** while taking Accutane and for 1 month after stopping Accutane. We do not know if Accutane can pass through your milk and harm the baby.

- **Do not give blood** while you take Accutane and for 1 month after stopping Accutane. If someone who is pregnant gets your donated blood, her baby may be exposed to Accutane and may be born with birth defects.

- **Do not take other medicines or herbal products** with Accutane unless you talk to your doctor. See "What should I tell my doctor before taking Accutane?".

- **Do not drive at night until you know if Accutane has affected your vision.** Accutane may decrease your ability to see in the dark.

- **Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using Accutane and for at least 6 months after you stop.** Accutane can increase your chance of scarring from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.

- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. Accutane may make your skin more sensitive to light.

- **Do not share Accutane with other people.** It can cause birth defects and other serious health problems.

What are the possible side effects of Accutane?

- **Accutane can cause birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births.** See **"What is the most important information I should know about Accutane?"**

- **Accutane may cause serious mental health problems.** See **"What is the most important information I should know about Accutane?"**

- **serious brain problems.** Accutane can increase the pressure in your brain. This can lead to permanent loss of eyesight and, in rare cases, death. Stop taking Accutane and call your doctor right away if you get any of these signs of increased brain pressure:
  - bad headache
  - blurred vision
  - dizziness
  - nausea, or vomiting
  - seizures (convulsions)
  - stroke

- **stomach area (abdomen) problems**. Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Accutane. Stop taking Accutane and call your doctor 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
  - dark urine

- **bone and muscle problems.** Accutane may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your doctor if you plan hard physical activity during treatment with Accutane. Tell your doctor if you get:

  - back pain
  - joint pain
  - broken bone. Tell all healthcare providers that you take Accutane if you break a bone.

  Stop Accutane and call your doctor right away if you have muscle weakness. Muscle weakness with or without pain can be a sign of serious muscle damage.

  Accutane may stop long bone growth in teenagers who are still growing.

- **hearing problems.** Stop using Accutane and call your doctor if your hearing gets worse or if you have ringing in your ears. Your hearing loss may be permanent.

- **vision problems.** Accutane may affect your ability to see in the dark. This condition usually clears up after you stop taking Accutane, but it may be permanent. Other serious eye effects can occur. Stop taking Accutane and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant. If you wear contact lenses, you may have trouble wearing them while taking Accutane and after treatment.

- **lipid (fats and cholesterol in blood) problems.** Accutane can raise the level of fats and cholesterol in your blood. This can be a serious problem. Return to your doctor for blood tests to check your lipids and to get any needed treatment. These problems usually go away when Accutane treatment is finished.

- **serious allergic reactions.** Stop taking Accutane and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your doctor if you get a fever, rash, or red patches or bruises on your legs.

- **blood sugar problems.** Accutane may cause blood sugar problems including diabetes. Tell your doctor if you are very thirsty or urinate a lot.

- **decreased red and white blood cells.** Call your doctor if you have trouble breathing, faint, or feel weak.

The common, less serious side effects of Accutane are dry skin, chapped lips, dry eyes, and dry nose that may lead to nosebleeds. Call your doctor if you get any side effect that bothers you or that does not go away.

These are not all of the possible side effects with Accutane. Your doctor or pharmacist can give you more detailed information.

How should I store Accutane?

- Store Accutane at room temperature, between 59° and 86°F. Protect from light.
- **Keep Accutane and all medicines out of the reach of children.**

General Information about Accutane.

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Accutane for a condition for which it was not prescribed. Do not give Accutane to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Accutane. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Accutane that is written for health care professionals. You can also call iPLEDGE program at 1-800-495-0654 or visit www.ipledgeprogram.com.

What are the ingredients in Accutane?

Active Ingredient: Isotretinoin

Inactive Ingredients: beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

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

Dilantin is a registered trademark of Warner-Lambert Company LLC.

Distributed by:

Pharmaceuticals

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

27898954

Revised: August 2005

[text printed on 'prescription pak' blister cards]

Accutane (isotretinoin capsules)

IMPORTANT INFORMATION FOR ALL PATIENTS:

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

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

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

You should read, understand and sign a Patient Information/Informed Consent form before you take Accutane. Contact your doctor if you have not signed this form (male patients and female patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

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

Before you start taking Accutane, tell your doctor if you:

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

Special Warning for Female Patients

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

Accutane causes serious birth defects. Do NOT take Accutane if you are pregnant.

It is very important for you to read and understand the information about preventing pregnancy found in this package, the Medication Guide, and the materials given to you by your doctor. It is very important for you to interact with the iPLEDGE system to answer questions about program requirements and view the DVD at your doctor's office. If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Accutane. Call your doctor.

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

Mental problems and suicide

Some patients have become depressed or developed other serious mental problems while they were taking Accutane or shortly after stopping Accutane. Some patients taking Accutane have had thoughts of ending their own lives (suicidal thoughts). Some people have tried to end their own lives (attempted suicide) and some people have ended their own lives (committed suicide). There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these problems or behaviors or if they would have happened even if the person did not take Accutane.

Stop taking Accutane and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

- 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 guilt.
- Start having thoughts about hurting yourself or taking your own life (suicidal thoughts).
- Start acting on dangerous impulses.
- Start seeing or hearing things that are not real.

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

Other serious side effects to watch for

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

- Headaches, nausea, vomiting, blurred vision (increased brain pressure).
- Severe stomach pain, diarrhea, rectal bleeding, or trouble swallowing.
- Yellowing of your skin or eyes and/or dark urine.
- Changes in hearing.
- Allergic reactions (if you know you are sensitive to "parabens", tell your doctor because it is a preservative in the gelatin capsule of Accutane).

- Bone or muscle pain.
- Vision changes, including trouble seeing at night (this can start suddenly, so be very careful when driving or operating any vehicle at night).
- Persistent fever, chills, or sore throat.

Other Important Information is found in the Medication Guide and in the booklets from your doctor:

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

Accutane Causes Serious Birth Defects

[text appearing on main back panel outside of card]

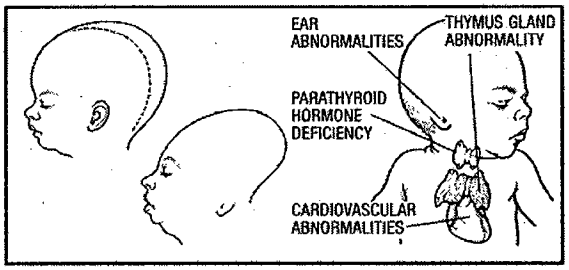
Highlights of Warning to Female Patients. (It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- You MUST NOT take Accutane if you are pregnant because any amount can cause severe birth defects, even if taken for short periods during pregnancy.
- You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking Accutane.
- You will not get your first prescription for Accutane until there is proof you have had 2 negative pregnancy tests as instructed by your doctor (a negative test means that it does not show pregnancy) and you have interacted with the iPLEDGE system to answer questions about program requirements.
- You cannot get monthly refills for Accutane unless there is proof that you have had a negative pregnancy test conducted in a lab every month during Accutane treatment.
- Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control must be used at the same time for at least 1 month before, during, and for 1 month after you stop taking Accutane.
- Stop taking Accutane right away and call your doctor immediately if you have sex without birth control, miss your period or think you are pregnant while you are taking Accutane. If you think you are pregnant in the month after you have stopped Accutane treatment, call your doctor immediately.

Very severe birth defects have occurred with Accutane use including:

• **Severe Internal Defects:** defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.

• **Severe External Defects:** defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.



[illustration of how to remove capsules]

Figure A

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

[binder copy]

FEMALE PATIENTS: xx MG
DO NOT GET PREGNANT

27898956
27898958
27898960

Revised: August 2005

Accutane Revised Text for Blue Boxes on Outer Cartons

Accutane (isotretinoin capsules)

Special Instructions to Pharmacists:

- Only fill Accutane after authorization from the iPLEDGE program by calling 1-866-495-0654 or visiting www.ipledgeprogram.com
- Dispense no more than a 30-day supply
- An Accutane Medication Guide is included in each Prescription Pak
- Dispense Prescription Paks intact
- Do not remove Prescription Paks from carton until dispensed

Reminders for Pharmacists:

- Dispense isotretinoin only for registered patients after obtaining authorization from the iPLEDGE program by calling 1-866-495-0654 or visiting www.ipledgeprogram.com
- Write Risk Management Authorization number on the prescription
- Dispense no more than a 30-day supply. No refills.
- Dispense Prescription Paks intact
- Do not dispense after the "Do not dispense to Patient After" date
- A Medication Guide is included in each Prescription Pak

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-662 / S-056

MEDICAL REVIEW

Division Director's Review Memorandum of NDA 18-662
SLR 056

August 11, 2005

I will not recount the regulatory history or most of the observations on the iPLEDGE Program which are conveyed in the Medical Officer's review of NDA 18-662 (SLR 056) by Dr. Jill Lindstrom, signature date August 11, 2005.

It is anticipated that the sponsor will be requesting approval of the new labeling, which includes, but is not limited to, provisions for iPLEDGE, under Subpart H (314.500-560). As stated in the new boxed warning, Accutane will be approved for marketing only under a special restricted distribution program. To be fully successful, the new iPLEDGE Program would need to provide convincing evidence that:

1) no isotretinoin product is available for dispensing outside of the iPLEDGE Program,
2) no pregnant women are started on isotretinoin, and
3) conceptions (and, thus, fetal exposure) during isotretinoin therapy and in the month following discontinuation of isotretinoin therapy should approach zero.

Under the S.M.A.R.T. Program, isotretinoin was dispensed to patients upon presentation of a written prescription with a yellow adhesive qualification sticker from the prescribing physician that signified to the pharmacist that the patient was not pregnant. However, sometimes stickers were placed on prescriptions without pregnancy testing being done to ensure that the patient was not pregnant. Under the iPLEDGE Program, instead of a yellow sticker, the prescribing physician or a designated office staff person will enter into a computer-based system the assertion that a negative pregnancy test was obtained. As with the yellow sticker, a computer entry does not ensure veracity; however, the registration and education of patients should make them more aware that a specimen for a pregnancy test should have been obtained. This awareness may incentivize greater compliance.

While the program currently is not sufficient to guarantee that no isotretinoin product will be available for dispensing outside of iPLEDGE, the Compliance Evaluation Plan is likely sufficient to direct subsequent program upgrades.

The new labeling also reflects FDA's continued attention to the possibility of a causal relationship between isotretinoin and psychiatric adverse events. A broader assessment of the psychiatric events and the sufficiency of labeling for psychiatric risk will occur in the near future.

In sum, iPLEDGE Program offers the possibility of better risk management than with S.M.A.R.T. Program. The approval of SLR 056 represents the beginning of a

process to flesh out further details of the iPLEDGE Program providing for even greater risk management.

Recommendation:

I recommend approval of this labeling supplement under Subpart H with the understanding that the sponsor will continue to improve the Process Compliance Evaluation Plan as needed.

Jonathan Wilkin, M.D.
Director, Dermatologic and
Dental Products

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

/s/

Jonathan Wilkin
8/11/05 05:46:27 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: August 12, 2005

FROM: Florence Houn MD MPH

SUBJECT: Office Director's Memo

TO: NDA 18-662 Accutane (isotretinoin) Supplement 056

This memo documents my decision to approve the above supplemental application under 21 CFR 314.520, provisions for restrictions for safe use.

Introduction

Isotretinoin is highly teratogenic. Skull, facial, and internal organ deformities, some leading to death, have been reported in children whose mothers used isotretinoin and carried their fetuses to term. More than 70% of women who became pregnant on isotretinoin choose abortion. Of the live births exposed in utero to isotretinoin, a quarter to a third will have major malformations. The human burden of this drug in the U.S. in 2005 is estimated to be up to 300 pregnancy exposures each month[i].

The drug's approved indication is for the "treatment of severe recalcitrant nodular acne" and "...should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics." This indication represents a serious illness because in addition to being painful and disfiguring, it causes permanent scarring which can have devastating impact on social, psychological and emotional functioning. The dermatologists in the review division agree this is a serious illness along with the American Academy of Dermatology as well as the practicing medical community and patient advocacy groups with inflammatory skin disorders (see below). The drug provides a meaningful therapeutic benefit to patients who fail existing conventional therapy. There are no other drugs approved for this indication. 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.

Over the 23 years of marketing, FDA has used risk communication and risk management strategies through a series of progressive steps: boxed WARNINGS and CONTRAINDICATIONS, informed consent, and registration of physicians to obtain qualification stickers to be placed on prescriptions to identify patients who have negative monthly pregnancy testing. These steps attempted to lower the numbers of pregnancy exposures, but exposure to drug during pregnancy has continued. Further action is needed. The most recent risk management program was SMART (generics had similar programs), and it used stickers on prescriptions to signify to pharmacists that the patient was not pregnant. In a prescription compliance survey done by Hoffman LaRoche and a survey of branded isotretinoin (Accutane) user volunteers done by Sloan Epidemiology Unit and, starting in 2002, and then by Degge/ SI thereafter, 5,469 respondents were randomly selected and queried.[ii] During the year before SMART and the year with SMART, 127 and 120 fetuses were exposed, many resulting in termination, both pre- and post-SMART. This occurred in the face of a 23% decline in new prescriptions during SMART. Thus labeling and agreed upon risk management programs designated as a condition of approval in FDA action letters did not ensure safe use.[iii]

On December 10, 2003, the acting CDER Center Director and key FDA officials met with the manufacturers of isotretinoin before the public advisory committee meeting to let the manufacturers know that there had been no change in pregnancy exposure rates in a sample survey pre-SMART and post-

SMART and that a single risk management program was needed.[iv] The February 26 and 27, 2004, the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee viewed the SMART program, the similar generic manufacturers' sticker program, and Agency's past efforts as insufficient and recommended a mandatory program of all registered parties be implemented. The new industry proposal for risk minimization action plan (RiskMAP) is called iPLEDGE and involves registration of patients, physicians, pharmacists, and wholesalers interacting with a voice-activated system to allow real time access to pregnancy information.

IPLEDGE further links access to the drug only in the case of negative pregnancy testing results, where upon physicians, patients, pharmacists, and wholesalers are registered and end-users (patients, pharmacists, and prescribers) interact with a technology-based system. Registered, activated prescribers enter a women's pregnancy testing results monthly in the system, and registered, activated pharmacists access the program via phone or internet to determine whether the patient is also registered and authorized to receive isotretinoin (based on current negative pregnancy testing and current patient-identified use of contraception or abstinence) prior to dispensing the drug. A pregnancy registry will be established with follow up to analyze root cause of failure. This entire new program is specifically modeled after the program to prevent pregnancy exposure while on thalidomide, a drug approved under Subpart H for a skin condition less likely to cause permanent sequelae and with lower overall risk for teratogenicity given the shorter duration of the teratogenic vulnerable period in pregnancy and absolute lower numbers of patients of child bearing potential using thalidomide.

Although the new isotretinoin risk minimization program is agreed to voluntarily by both the innovator and generic sponsors, there is concern that to best protect the public health, the application be approved under 21 CFR 314.520 (Subpart H). Approval under Subpart H shows the Agency is using its full regulatory muscle to ensure safe use. Key safety components of the RiskMAP are not in labeling such as the program's criteria for de-enrollment of non-compliant registered participants, do not require prior agreement supplements and could be modified without Agency participation. Furthermore, Subpart H has advantages of advanced promotional materials review, application to generics, and expedited withdrawal.

Clinical Issues

Risk of Teratogenicity: Relative and Absolute Risk

Isotretinoin is a potent human teratogen during the first trimester of pregnancy. There is no time during gestation when exposure to isotretinoin is known to be safe; the vulnerability period to a fetus extends throughout gestation. The pharmacokinetics of this drug shows a half life of 24 hours. It will take two weeks for 99% of the drug to clear. There is no known safe exposure concentration to isotretinoin for the fetus during the vulnerable period. In contrast, the period of teratogenic risk for thalidomide is 15 days long (from day 35 to day 50 of pregnancy). The half-life of thalidomide is 5 to 7 hours. After 24 to 48 hours, the drug is not detectable after dosing. Thus, both the period of vulnerability for teratogenicity and the amount of time for elimination of the drug from the last dose are longer for isotretinoin than for thalidomide.

Thalidomide was approved under Subpart H for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations. This is a reactional state that occurs with treatment in a subset of leprosy patients (borderline lepromatous or lepromatous leprosy patients). Thalidomide is restricted because of teratogenicity. It is estimated there are about 5,000 patients per month using thalidomide, but only about 5% (250) of these patients are females of childbearing potential. About 90% of use of thalidomide is for off-label uses in diseases where child-bearing potential is less. For example, the major uses of thalidomide are for multiple myeloma, renal cell cancer, and malignant melanoma, diseases that occur in older patients. The average age of patients on thalidomide is 66 years old (female mean age is 42). Since marketing, under the thalidomide restricted distribution plan, there has only been one pregnancy report. This woman had 3 consecutive weekly pregnancy tests which were negative prior to the test at week 4 being positive. She had a spontaneous miscarriage.

In contrast, isotretinoin is used for the entire spectrum of acne, from the serious and severely affected nodular acne patients, to the mild to moderate acne vulgaris patients. The use of isotretinoin is nearly evenly distributed between male and female patients. There are over 30,000 women getting isotretinoin each month. Only 7.1% of female patient users were over age 45, while the remaining 92.9% were of ages well-within child-bearing potential (93% of 30,000 is 27,900 women of child bearing potential getting isotretinoin monthly). Dr. Allen Brinker of the FDA Office of Drug Safety estimates the isotretinoin pregnancy exposure rate is about 1 per 100 women of childbearing potential per month. Dr. Allen Mitchell, of Sloan Epidemiology Unit, estimates the risk is about 1 in 10,000 women per month. Regardless of what estimate is accurate, FDA has received approximately 2,000 reports of pregnancy exposure, congenital abnormalities, and reports of abortion since marketing.[v] Recently there is concern for neurologic and cognitive effects of drug in children with in utero exposure without malformations. Thus, the amount of days at risk and the absolute risk given the total population of females of childbearing potential being greater, is higher with isotretinoin compared to thalidomide, approved under Subpart H for restrictions for safe use due to teratogenicity.

Use Data and Population Magnitude of Risk

During the SMART program from April 2002 to March 2003, there were 1.16 million prescriptions dispensed, approximately 80% written by dermatologists. About half the prescriptions were for women, and 93% of these were under age 45. The current sponsors estimate that there are approximately 60,000 patients a month use isotretinoin. Thus, about 27,900 women of child bearing potential a month are at risk for being pregnant on isotretinoin. Between 1 per 100 to 1 per 10,000 women of child bearing potential become pregnant while taking isotretinoin. FDA has received approximately 2,000 reports since marketing of these pregnancy exposures (the number of reports will be less than actual pregnancy exposures due to underreporting). In contrast, for thalidomide teratogenic exposure, it is estimated approximately 250 women of childbearing potential are at risk per month for getting pregnant while on thalidomide. Only one report of pregnancy while on thalidomide has ever been reported since approval in 1998.

Seriousness of Indication

Acne vulgaris is a common, chronic inflammatory disease of the pilosebaceous follicle which affects 85% of adolescents and may persist into adulthood. The face, chest and back are the main body areas affected. Acne can range in severity from mild, consisting of a few comedoes or non-inflammatory lesions, to severe, with large painful nodules, smaller papules, pustules and comedones, and permanent scarring[vi]. Isotretinoin is indicated for severe, recalcitrant nodular acne which has not responded to oral antibiotics. Clinically, nodules are large (5mm or greater), raised, erythematous, tender lesions which may be fluctuant, hemorrhagic or crusted. Nodules can persist for months and resolve with permanent scars.

Acne causes significant social, psychological and emotional impairment. Lasek and Chen used Skindex, a validated 29-item instrument, to measure the effects of skin disease on patients' quality of life. In their study, acne patients report emotional effects from their skin disease similar in magnitude to those reported by patients with psoriasis, a skin condition recognized to cause significant disability.[vii] Patients diagnosed with severe acne reported worse quality of life than patients diagnosed with moderate or mild acne, and older patients reported worse scores than younger patients. Mallon, et. al., compared quality of life of acne patients with that of patients with non-dermatologic illnesses using two different instruments, the General health questionnaire (GHQ-28) and the Short Form 36 (SF-36). The found that acne patients had worse scores for mental health and social function than patients with asthma, epilepsy, diabetes, back pain, and arthritis, and worse scores for role limitation for emotional reasons than patients with asthma,

epilepsy, back pain, and arthritis.[viii] Finally, Newton et al., using the DLQI and GHQ-28, noted that the impaired self-esteem, social function, mental health, energy/vitality and pain reported by acne patients prior to treatment improved after treatment, and that the improvements were greater in patients treated with isotretinoin than in those treated with antibiotics.[ix]

As discussed in the preamble to the proposed accelerated approval rule (57 FR 13234, April 15, 1992), determination of the seriousness of a condition: ... is a matter of judgment, but generally is based on its impact on such factors as ... day-to-day functioning, or the likelihood that the disease, if left untreated, will progress..." Severe recalcitrant nodular acne significantly reduces quality of life, and impairs emotional, social and psychological functioning. Additionally, severe recalcitrant nodular acne causes permanent scarring and disfigurement, which worsens without treatment.

On February 27, 2004 the American Academy of Dermatology, Society of Dermatology Physicians Assistants, and the Inflammatory Skin Diseases Institute, a patient advocacy group, called recalcitrant nodular acne unresponsive to conventional systemic therapies as a "serious medical condition."[x] The American Academy of Dermatology has made similar states at previous FDA Advisory Committee meetings (September 18, 2000, May 20, 1991 and May 8, 1989).

Criteria for Subpart H Met

FDA has publicly stated Recalcitrant Nodular Acne Unresponsive to Systemic Therapies is Serious

The Food and Drug Administration Talk Paper of October 31, 2001 stated: "Accutane is approved to treat the most serious form of acne. This form is painful, permanently disfiguring, and does not respond to other acne treatments. Accutane is very effective, but its use carries significant potential risks, including birth defects and even fetal death."

The 2005 FDA Patient Information Sheet says: "Isotretinoin 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 acne, many red, swollen, tender lumps form in the skin. If untreated, nodular acne can lead to permanent scars." [xi]

At the September 19, 2000 Dermatologic and Ophthalmic Drugs Advisory Committee meeting, the FDA's CDER Dermatologic and Dental Drug Products Division Director, Jonathan Wilkin, stated: "...Accutane is uniquely effective for severe cystic acne, a mutilating, scarring condition that can severely compromise the quality of life (p.35)....Not only can Accutane induce remission, unlike any other therapy, it is also more effective in control than any other therapy (p.43)"[xii]

Furthermore, see the transcripts for February 26, and 27, 2004 joint Advisory Committee meeting, Day 1, pages 21-24 and corresponding slides, Dr. Jill Lindstrom, Team Leader for the FDA's CDER Division of Dermatology and Dental Products states: "This patient has nodular acne, a devastating disease that can result in significant scarring and permanent disfigurement....isotretinoin is unique among the therapies in the acne armamentarium in that it addresses all four of the known pathogenic mechanisms of acne...other anti-acne agents have no long-term impact and are effectively only while they are used."

Meaningful Therapeutic Benefit of Isotretinoin over existing therapies

The clinical trials demonstrate that the majority of patients were cured or in prolonged remission following only a single 15-20 week course of isotretinoin.[xiii] [xiv] [xv] Isotretinoin is indicated for patients who have failed other systemic therapies. There is no other drug approved for this indication. About 90% of patients who undergo a single course do not need further treatment with isotretinoin and can be maintained on other drugs with less risks. See above section, "FDA has Publicly Stated Recalcitrant Nodular Acne Unresponsive to Systemic Therapies is Serious" for quotes from FDA documents and officials stating isotretinoin's benefits are "very effective", "uniquely effective", and results in remission and control "unlike any other therapy."

The manufacturer, Hoffman LaRoche (HLR), requests approval of supplement under Subpart H

On August 11, 2005 Roche sent in a letter to FDA requesting approval under Subpart H.

Monitoring compliance with iPLEDGE requirements

The sponsors submitted, "Possible Data Sets for Compliance Monitoring," on August 1, 2005 that details the program's ability to assess aggregate data of units in and units out of wholesalers. Unfortunately, wholesalers have agreements with their pharmacies that pharmacy names and quantities received are not revealed to other parties and there is no standardization of data. On August 11, 2005, the sponsors (HLR and generics) submitted, "Agreements Needed for Compliance Evaluation Plan" and "One Strike Policy". Then, in the tcon that day, the sponsors explained that they would inform pharmacies that to register and activate, pharmacies should give permission to allow wholesalers to disclose identification information and amounts of drug received to iPLEDGE and delegates and FDA. We will meet the companies in September and October to see the level of pharmacy cooperation with this as pharmacies being registering in early September. If cooperation is low, sponsors were told they may need to pursue a different distribution mechanism and that can be submitted on November 12, 2005 with their Process Compliance Evaluation Plan.

At the pharmacy level, the sponsor described using IMS DDD and iPLEDGE data. DDD has units of drug shipped into pharmacies from wholesalers using 3 and 5 digit zip codes. Three digits are used for areas with 3 or fewer pharmacies. IMS must get pharmacies to give permission to share their names with manufacturers. I understood the IMS representative to have stated that the data are from 34,000 of the 55,000 US retail pharmacies (not hospital, not clinics, not doctor's offices, not outpatient departments, etc.). Kaiser and Walmart (4-5% of Rx) are not covered. Through IMS, Roche and other customers (not all the generics are IMS customers) can sit down with IMS and see their wholesalers, but no written documents are generated from IMS that contain names of wholesalers.

IMS Xponent data captures prescribers writing prescriptions of the drug (name of prescribers and number of prescriptions written). The lag time is about 10 days for weekly reports and 3 weeks for monthly reports. Xponent captures 75% of prescriptions of the overall market.

At the physician level, compliance with iPLEDGE requirements can be independently confirmed through a mechanism such as a chart review to check if pregnancy tests were ordered. Also, physician data on who wrote for isotretinoin from Xponent can be cross checked with iPLEDGE registration/activation information. The sponsors agree to propose such a plan.

At the patient level, independent compliance with iPLEDGE can also occur with a chart audit, if the sponsors are not amenable to an anonymous patient survey.

The agreements reached on August 11, 2005 are below and were acceptable to the Office of Compliance (see Dr. Susan Allen's memo August 11, 2005):

Elements for Wholesalers

- A plan to proactively audit wholesalers at a frequency agreed upon with FDA to identify a wholesaler who is in violation of the program. This plan should include a proposal agreed to by FDA to select a representative sample of wholesalers for such auditing if auditing of all wholesalers involved in iPLEDGE is not feasible.

- An agreement that a violative wholesaler will be subject to a one-strike policy and prohibited from selling product after a single infraction of the program. This should include a commitment from the sponsors to promptly investigate any wholesaler identified as selling the drug to an unregistered/non-activated pharmacy. A decision about whether to immediately deactivate a violative wholesaler prior to a full investigation of the violative behavior or to

allow continued activation of the wholesaler until an investigation has been completed will be dependent upon the amount of time the sponsors commit to performing such investigations.

- Sponsor Response: The sponsors propose a 4 week period to perform such an investigation.

- Roche will continue to submit to the Agency on a quarterly basis, an internet surveillance report with information on internet sites that advertise and claim to sell Accutane to customers in the United States. The other sponsors will continue to provide their report as discussed and agreed upon with the Agency.

- A wholesaler agreement and deactivation policy that clearly describe all iPLEDGE wholesaler responsibilities and consequences for failure to comply with the agreement.

Elements for Pharmacies

- Sponsor Goal: To investigate and work with pharmacies to implement the following:
  - To obtain agreement from pharmacies to allow wholesalers to disclose identification of pharmacies who have purchased isotretinoin product and in what quantity
- An agreement that if the sponsors become aware of a non-activated pharmacy dispensing, selling, buying, borrowing, loaning, or otherwise transferring isotretinoin in any manner outside of iPLEDGE, the sponsors will immediately follow-up and instruct the pharmacy to immediately return any remaining product that the pharmacy has in stock in order to prevent future dispensing by the pharmacy outside the RiskMAP.

- Provide data on general trends for units shipped in to registered and activated pharmacies versus prescriptions dispensed from registered and activated pharmacies to detect general imbalances on an aggregate level using data from iPLEDGE and from nationally validated and generally accepted data resources.

Elements for Patient Compliance

- Develop an independent means to audit patient compliance with:
  - For females of child-bearing potential, use of two effective forms of birth control
  - For females of child-bearing potential, monthly pregnancy testing
  - For females of child-bearing potential, monthly contraceptive counseling
  - For patients, signed patient information/informed consent.

Desired Elements for Prescribers

- Provide general trends to detect imbalances between registered and activated prescribers compared to actual prescribers on an individual prescriber level from nationally validated and generally accepted data resources.
- Develop a method to identify registered, activated prescribers who are not obtaining and inputting pregnancy testing results according to iPLEDGE

Product Tracking and System Compliance Review

- It is recommended that each sponsor plan to audit the activities of any third party contractors involved in the manufacture, packaging, testing or distribution of isotretinoin on an annual or biennial basis at a minimum.

- It is recommended that all isotretinoin sponsors ensure that their goods returned policies contain statements that violative pharmacies/wholesalers will be asked to return product.

Report Format

- It is recommended that the iPLEDGE program Evaluation Report format and content be submitted for agreement.

Finalized documents describing these systems are to be submitted by November 12, 2005 and will be implemented by January 1, 2006.

How psychiatric safety concerns are handled in this supplement

The consult on January 14, 2005 of Dr. Andrew Mosholder, Dr. Diane Wysowski, and Marilyn Pitts recommended insertion in the labeling of more specific advice on how dermatologists should monitor for and manage psychiatric disorders, additional studies to test the causal relationship of drug and psychiatric adverse events, and that psychiatric adverse events be reported to iPLEDGE program. The recommendation for labeling changes was accepted and Dr. Mosholder, Wysowski, and Pitts were the lead negotiators for the labeling on these issues. The clinical studies, as everyone acknowledged, would be difficult to conduct given unblinding effects of isotretinoin and no other treatment is effective for severe nodular acne. Finally, the iPLEDGE program has procedures for contacting patients and prescribers and will collect information on lost to follow up and drug discontinuations to find out the reason for stopping drug. The suggestion of a 3 or more possible multiple choice answers to the question of why is the patient no longer on drug or in iPLEDGE was rejected by the sponsor for 1) pregnancy and 2) other. If "other" is selected on line, the client must enter text to advance to the next screen to motivate more information gathering. The focus of iPLEDGE is pregnancy prevention, and this method of ascertainment of drug discontinuation is acceptable. An enhancement of putting in the patient registration section permission to contact an additional person for follow-up will be discussed again as a future upgrade for the system.

Generic Sponsors of Amnesteen, Sotret, and Claravis (isotretinoin)

The generic sponsors of isotretinoin were involved in negotiations of the iPLEDGE RiskMAP during the supplement cycle. There were weekly teleconferences with them on issues of compliance with metrics, patient educational materials, and they were kept appraised of the labeling negotiations by HLR. Subpart H approval applies to generics and they must follow the same restrictions for safe use.

For Future Discussion

Several items were discussed with the sponsor and placed on an agenda for future discussions because either incorporation at this point would delay roll out on December 31, 2005 for patients, or, evaluation is needed to determine whether the change is indicated. I list them for the record.

- Distribution System: As noted above, should an inadequate number of pharmacies not permit disclosure of identification information and amount of isotretinoin shipped by wholesalers to FDA, sponsors or delegates, we will revisit the need to restructure product flow for monitoring enhancement. We should know by November 12, 2005 if a new model of product flow is needed.
- Reasons for discontinuation of drug and lost to follow-up: We should revisit the tools for collection of this information if insufficient data can be retrieved from text inputted. Also, adding permission for patients to provide additional contact personnel to assist in follow up ascertainment will be rediscussed.
- Veterinarians: We discussed with the sponsors and at this point, veterinarians and animal patients are not accommodated in iPLEDGE. CVM was informed of this.
- Calculation of the 7-days from the Office Visit: We discussed if we could allow for more time for patients to fill prescriptions by using the date of pregnancy testing to begin the clock for needing to fill the prescription for females of child bearing potential. This would allow more time for these patients because some patient may delay testing after the office visit. The office visit start time for males and women who could not get pregnant would remain. This was discussed with the sponsor and at this time the complexity of the programming of the software and the changes in all the educational materials would delay the December 31, 2005 start date, so this enhancement (recommended by the AADA) will be discussed later.

- Access to drug by patients and unintended consequences: Program evaluation using pregnancy rates, compliance with key requirements, access to drug, as measured by participation of patients, physicians, and pharmacies, as well as wholesalers, will need careful monitoring. The balance of achieving access versus ensuring safe and appropriate use will need constant evaluation. Lessons Learned after one year should be considers, as was done with Lotronex's Unintended Consequences Working Group.

All outstanding issues of the supplement have been satisfactorily addressed.

End Notes

[i] Brinker, Allen, FDA/CDER/ODS, email June 28, 2005.

[i] Brinker, A, Kornegay, C, Nourjah P. Trends in adherence to a revised risk management program designed to decrease or eliminate isotretinoin-exposed pregnancies: evaluation of the Accutane SMART program. Arch Dermatology. 2005;141:563-9.

[iii] FDA supplement approval letter signed by Jonathan K.Wilkin MD, October 30, 2001, NDA 18,662 Accutane (isotretinoin) Supplement #44.

[iv] Memorandum of Meeting, December 10, 2003, July 9, 2004 FDA White Paper "isotretinoin teratogenicity risk management program" sent to sponsors.

[v] Brinker A, Trontell A, Beitz J. Letter to the Editor, Journal American Acad Dermatol 2002;47: 798-9.

[vi] James WD. Acne. N Engl J Med 2005. 352;14:1463-71

[vii] Lasek RJ, Chren MM. Acne Vulgaris and the Quality of Life of Adult Dermatology Patients. Arch Dermatol 1998; 134(4):454-458.

[viii] Mallon E, Newton JN, et. al. The Quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999; 140:672-676.

[ix] Newton JN, Mallon E, et. al. The effectiveness of acne treatment: an assessment by patients of the outcome of therapy. Br J Dermatol 1997; 137:563-567.

[x] Transcipt of Joint meeting of the Drug Safety and Risk Management Advisory Committee and Dermatologic and Ophthalmic Drugs Advisory Committee, Feb. 27, 2004. Pp. 23-24, 26, and 32.

[xi] http://www.fda.gov/cder/drug/InfoSheets/patient/isotretinoinPIS.pdf May 2005.

[xii] Dermatologic and Dental Drugs Advisory Committee meeting, September 18, 2000. http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3639t1a.pdf

[xiii] Peck, GL, Olsen, TG, Yoder FW, et al. Prolonged remissions of cystic and conglobate acne with 12-dis-retinoid acid. NEJM 1979; 300:329-333.

[xiv] Pochi PE, Shalita AR, Strauss JS, Webster SB. Report of the consensus conference on acne classification. J AM Acad Derm 1991; 24:495-500.

[xv] Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoic acid: evaluation of sebum production and the clinical response in a multiple-dose trial. J Am Acad Derm 1980;3:602-11.

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

/s/

Florence Houn
8/12/05 08:33:45 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 18-662
SLR 056

Correspondence date: June 24, 2005
Sponsor: Hoffmann-La Roche Inc
Established name: Accutane
Trade name: isotretinoin
Route of Administration: oral
Dosage Form: capsules
Indication: severe recalcitrant nodular acne
Review start date: August 6, 2005
Review completion date: August 7, 2005
Revision date: August 11, 2005

Regulatory History:
Accutane was approved for marketing on May 7, 1982. Because of a non-clinical signal for teratogenesis, Accutane was labeled as Pregnancy Category X and contraindicated for women who were or might become pregnant; information about the risk and prevention of fetal exposure was included in the CONTRAINDICATIONS, WARNINGS and PRECAUTIONS sections. The label was successively updated as human teratogenesis data accrued. A boxed warning was added on February 20, 1984, which recommended pregnancy testing prior to Accutane initiation and use of contraception for the month prior to therapy. Education and reminder tools such as Dear Doctor and Dear Pharmacist letters were issued, and pharmacists were instructed to affix red warning stickers to all Accutane prescriptions dispensed and to include a patient information brochure with the prescription. In 1986, instruction to begin Accutane therapy on the second or third day of the next menses following obtainment of a negative pregnancy test was added to the boxed warning.

In 1988, the sponsor introduced the Accutane Pregnancy Prevention Program, a risk management program that strengthened the content of labeling and added new education and reminder tools as well as assessment surveys. In the APPP, the boxed warning advised obtainment of a negative serum pregnancy test within two weeks prior to onset of therapy, use of two reliable forms of contraception simultaneously for one month before, during, and one month following discontinuation of therapy, initiation of therapy on the second or third day of the next menses following confirmation of non-pregnant status, monthly repetition of contraception counseling and pregnancy testing, and use in women of child bearing potential only if the patient had severe disfiguring cystic acne recalcitrant to standard therapies and was reliable in understanding and carrying out instructions. Education tools and targeted outreach included two Dear Doctor letters and patient brochures. New reminder tools were introduced: the blister pak with the "Avoid Pregnancy" icon, a limitation of amount dispensed to 30-days supply, and patient informed consent forms. A voluntary patient survey and a prescriber survey were instituted to assess prescriber and patient compliance with the APPP.

In September 2000, the Dermatologic and Ophthalmologic Drugs Advisory Committee (DODAC) convened to discuss risk minimization of fetal exposure to Accutane. DODAC articulated two goals: 1) that no woman should begin isotretinoin therapy if pregnant, and 2) that no woman become pregnant while being treated with isotretinoin. DODAC recommended strengthening of the APPP by augmentation of patient education, registration of patients and prescribers, implementation of a pregnancy registry, and linkage of prescription dispensing to adequate pregnancy testing.

In response to the DODAC recommendations, the current riskMAP, S.M.A.R.T., was approved for the innovator on October 30, 2001 (SPIRIT, IMPART, and ALERT are the identical [except for tradename] riskMAP programs for the generic forms of isotretinoin), and roll-out was completed on April 14, 2002. In addition to continuing the content and tools of the APPP, S.M.A.R.T. added a requirement for a second pregnancy test within the first five days of menses prior to starting therapy, and a new reminder tool, a qualification sticker, intended to link prescribing of isotretinoin to demonstration of adequate pregnancy testing. A Medication Guide is dispensed with the drug. The voluntary patient survey was continued, and a pharmacy survey replaced the prescriber survey.

In February 2004, a joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and DODAC convened to review data from the first year after implementation of SMART. In brief, the number of reported isotretinoin-exposed pregnancies did not decrease from the year prior to SMART's implementation. Additionally, although sticker use was high, it was an imperfect surrogate for pregnancy testing, and participation in the voluntary patient survey, approximately 25%, was significantly below the agreed-upon benchmark of 60%. The combined committee found that four separate sets of program materials were confusing and made metrics difficult to assess. They recommended strengthening and consolidation of the isotretinoin riskMAP, to include registration of all patients, prescribers and pharmacies, tighter linkage of pregnancy testing to prescription dispensing, implementation of a pregnancy registry, and participation of all manufacturers in a single riskMAP.

Current Submission:

iPLEDGE Components of Labeling

Revised package insert

- Professional labeling
- Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)
- Patient Information/Informed Consent (for all patients)
- Medication Guide

Packaging

- Blister card

- Carton

Prescriber Educational Materials
- iPLEDGE Program Guide to Best Practices for Isotretinoin
- iPLEDGE prescribing checklist for female patients of child bearing potential
- iPLEDGE prescribing checklist for male patients and female patients who cannot get pregnant
- iPLEDGE program prescriber contraception counseling guide
- iPLEDGE program contraception referral form and contraception counseling guide
- Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin

Pharmacy Educational Materials
- The iPLEDGE Program Pharmacist Guide for Isotretinoin

Patient Educational Materials
- IPLEDGE Program Patient Introductory Information Brochure
- IPLEDGE Program Guide to isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant
- IPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant: The Importance of Avoiding Pregnancy on Isotretinoin
- IPLEDGE Program birth Control workbook
- Patient DVD: Be Prepared, Be Protected and Be Aware: The Risk of Pregnancy While on Isotretinoin

Other Materials
- Patient ID Card
- Prescription Bag Sticker

iPLEDGE Elements

In the current submission, the innovator, having worked with the generic sponsors of isotretinoin, has proposed iPLEDGE: a single, strengthened riskMAP for all marketed isotretinoin products. This consolidated, strengthened riskMAP builds on the prior programs by incorporating essentially all of the content and tools (education and reminder tools) of the current riskMAPs (SMART, SPIRIT, IMPART, ALERT), and adds to them a performance-linked access system and a pregnancy registry. Embedded in the performance-linked access system are the components of wholesaler, pharmacy, prescriber and patient registration (and activation).

Performance-Linked Access System

An essential element of the iPLEDGE program is the iPLEDGE system, a performance-linked access system (PLAS) which tightly links the dispensing of isotretinoin (for female patients of child bearing potential) to documentation of a negative pregnancy test,

as well as to prescriber confirmation that contraceptive counseling has occurred and prescriber and patient identification of contraceptive methods chosen. The iPLEDGE system also provides an opportunity to reinforce patient education through "testing" of contraceptive knowledge. The iPLEDGE system is a technology-based construction which can be accessed either via the internet or by phone. Access to the iPLEDGE system is restricted to registered prescribers, pharmacies and patients. This is to ensure that only prescribers registered and activated in iPLEDGE can prescribe isotretinoin, only pharmacies registered and activated in iPLEDGE can dispense isotretinoin, and only patient registered and qualified in iPLEDGE can receive isotretinoin.

Reviewer comments:

1. *A PLAS is the most restrictive tool available for risk minimization. Because the combination of education, outreach and reminder tools that comprise the current and prior riskMAPs did not adequately prevent fetal exposure to isotretinoin, addition of a PLAS to the tools already in place is justified, despite the burden it may impose on stakeholders.*
2. *The innovator and generic sponsors have collaborated to develop a single consolidated PLAS-based riskMAP for all marketed isotretinoin products. Although addition of a PLAS represents an increase in complexity and stakeholder burden compared to the current isotretinoin riskMAPs, this is offset by the simplification achieved by consolidation of the individual riskMAPs currently in place (SMART, SPIRIT, ALERT, IMPART) into a single program, iPLEDGE. Prescribers, pharmacies and patients will only need to navigate a single program, even if the patient switches brand during the course of therapy, which will reduce confusion and eliminate a source of patient dropout.*

Stakeholder Registration

Wholesalers, pharmacies, prescribers and patients must each register with the iPLEDGE program in order to distribute, dispense, prescribe or receive isotretinoin, respectively. Registration of these parties is intended to ensure that isotretinoin is not dispensed outside of the iPLEDGE program and hence potentially without protection against fetal exposure. Although prescribers are registered in the current riskMAP, registration by wholesalers, pharmacies and patients is new in iPLEDGE.

Wholesalers

Wholesalers, distributors and chain pharmacy distributors must register with iPLEDGE and agree to abide by relevant riskMAP procedures. Registration is accomplished by signing an annual agreement that they will only ship to registered pharmacies and will provide product flow data to the sponsor/s.

Wholesalers are not involved in the current riskMAP, S.M.A.R.T. However, under the restricted distribution plan of iPLEDGE, wholesaler registration and participation is essential to track product and ensure that diversion of product to non-iPLEDGE participating sources does not occur.

Reviewer comment: The sponsors estimate that approximately 90 to 100 wholesalers participate in the distribution of isotretinoin. Registration with iPLEDGE and

compliance with its procedures are essential to ensure that product is not diverted to venues which do not participate in the riskMAP.

Pharmacies
In contrast to S.M.A.R.T., in which any pharmacy may dispense isotretinoin (after ensuring that a yellow sticker is in place and correctly completed), in the iPLEDGE program only pharmacies that register and activate may access the iPLEDGE system, confirm patient qualification and dispense isotretinoin. Activation requires that the registered site pharmacist attest to possession of relevant competencies necessary to safely dispense the drug and agree to train other pharmacists on iPLEDGE and comply with iPLEDGE procedures. Pharmacy activation must be renewed annually.

Prescribers
Analogous to S.M.A.R.T., prescribers must register in order to receive iPLEDGE materials. After reviewing the materials, attesting to possession of relevant competencies, and agreeing to comply with iPLEDGE program requirements, prescibers are activated and may access the iPLEDGE system. Activation must be renewed annually. Only prescribers who are registered and activated with iPLEDGE (or their office staff designee) may register patients, confirm that counseling has occurred, and enter pregnancy test results. Prescribers must interact with the iPLEDGE system each month for both male and female patients in order for the patient to be qualified to receive isotretinoin.

Patients
In iPLEDGE, all patients, both males and females, must be registered as part of the qualification process order to receive isotretinoin. Registration involves assignment of an ID number, obtainment of informed consent (to include HIPAA), and input of demographic data (name, address, phone number, DOB, last four of SSN, patient ID number) into the iPLEDGE system The 2004 joint advisory committee recommended registration of patients of both genders. Patient registration is not a component of S.M.A.R.T.

Reviewer comments:

1. *Patient registration will provide the denominator for calculation of adverse event rates.*
2. *Registration of patients of child-bearing potential and patients not of child-bearing potential simplifies the program by not requiring pharmacists to follow different steps based on a patient's gender. Additionally, registration of both categories of patients positions the program to allow for potential program extension into neuropsychiatric risk minimization.*
3. *Demographic data will facilitate follow contact-up of patients who terminate therapy prematurely or report a pregnancy exposure.*
4. *Unlike the voluntary patient survey in S.M.A.R.T., patient registration will provide limited data on all patients in the riskMAP. However, patient compliance will not be assessed by the iPLEDGE system.*

Qualification of Female Patients of Child-Bearing Potential

Qualification of female patients of child-bearing potential under iPLEDGE is similar to qualification of such patients under S.M.A.R.T., but differs in four ways. First, in iPLEDGE, the second confirmatory pregnancy test and each monthly follow-up pregnancy test must be performed at a CLIA-certified laboratory. As in S.M.A.R.T., the test may be performed on urine or serum samples and must have a sensitivity of 25 mIU. Second, the prescriber must confirm each month in the iPLEDGE system that contraceptive counseling has occurred. Monthly contraceptive counseling is required in S.M.A.R.T., but the specific documentation that it has occurred is new in iPLEDGE. Third, both the prescriber and the patient must enter into the iPLEDGE system the primary and secondary form of contraception that the patient has selected. The primary form entered by the prescriber and patient must be an acceptable form and must match or the patient will not be qualified. The secondary form must be an acceptable secondary form (or a second primary form), but concurrence is not required between the secondary forms identified by the prescriber and the patient. The iPLEDGE requirement for use of two acceptable forms of contraception, a primary and a secondary form, parallels the contraceptive requirements of S.M.A.R.T., however the need for both the prescriber and the patient to document the patient's primary and secondary forms is new, as is the requirement for concurrence on the primary form identified. Fourth, the patient must correctly answer questions intended to reinforce key messages about the iPLEDGE program.

Reviewer comments:

1. *The requirement for pregnancy testing in a CLIA-certified laboratory eliminates the possibility that a home pregnancy test will be ordered (but not done). Additionally, use of a CLIA-certified laboratory reduces the likelihood of laboratory error. Most importantly, the requirement to enter the laboratory result obtained from a CLIA-certified laboratory ensures that a pregnancy test will be obtained. This requirement alone has the potential to eliminate the fetal exposures which occur because isotretinoin therapy is initiated in women who are already pregnant, which represented ten percent of known fetal exposures in the first year of S.M.A.R.T.*
2. *It is hoped that the requirement to document monthly contraceptive counseling will ensure that such counseling occurs. Non-compliance with contraceptive requirements is likely the primary cause of fetal exposures to isotretinoin.*
3. *The requirement for both the prescriber and patient to enter the patient's primary and secondary forms of contraception may increase the quantity and frequency of contraceptive counseling that occurs. Additionally, the need to enter the two forms (and to have concurrence with the primary form) serves as educational reinforcement for the patient on the need for use of two forms of contraception.*
4. *The patient comprehension questions are also intended to reinforce patient education on contraceptive knowledge.*

Qualification of Male Patients and Female Patients Who Cannot Get Pregnant

Unlike female patients of child-bearing potential, male patients and female patient who cannot get pregnant (nFDBP) do not need to access the iPLEDGE system each month to

be qualified. Males and females not of child-bearing potential must be registered in the iPLEDGE system initially (done by the prescriber or prescriber designee), and the prescriber must interact with the iPLEDGE system each month to confirm that the patient understands iPLEDGE program requirements.

Reviewer comment: Although males and females not of child-bearing potential do not need to be counseled about contraception, it is imperative that they understand iPLEDGE program requirements and do not share their isotretinoin or give blood during or for 30 days after therapy.

Pregnancy Registry

Fetal exposures to isotretinoin will be followed through the iPLEDGE pregnancy registry to obtain information on outcomes. Additionally, root cause analysis will be conducted to identify underlying causes behind fetal exposure. As part of registration and activation in iPLEDGE, pharmacies, prescribers and patients agree to report known pregnancies to the registry.

Reviewer comments:

1. *The registry will provide the numerator for fetal exposure rates. Although underreporting may still be an issue, the call-center follow-up of patients who do not complete their expected course of therapy may improve reporting. The root cause analysis may provide insight into areas of the riskMAP that need further strengthening.*
2. *Root cause analysis will not provide information on compliance among patients who do not become pregnant. A voluntary survey could provide this information.*

Psychiatric Adverse Events

The reader is referred to this author's 1 April 2005 review of neuropsychiatric adverse events for fuller discussion of this topic. In this labeling supplement, three of the recommendations from that review will be implemented.

First, the back of the iPLEDGE patient identification card contains a list of symptoms of depression, with the instructions to stop isotretinoin and contact one's doctor right away if the symptoms occur.

Second, the WARNINGS and Patient Information sections of the Package Insert are updated to include explicit instructions to obtain a personal and family history for mental illness prior to initiation of isotretinoin therapy, to assess for the signs and symptoms of depression or other mental illness during therapy, and to discontinue isotretinoin and consider further intervention if symptoms or psychiatric adverse events occur.

Third, patients who discontinue therapy prematurely will be queried as to the reason for premature discontinuation. Although this element of iPLEDGE was developed to identify cases of pregnancy, it will also identify other adverse events which lead to premature discontinuation of treatment.

Additional Comments:
The boxed warning was simplified by removing the riskMAP program details and placing them in the PRECAUTIONS section.

Reviewer comment: By reducing the text contained in the box, the essential information about teratogenesis and the importance of avoiding fetal exposure to isotretinoin may be conveyed in a more impactive way.

Recommendations:

1. Approval of the labeling supplement, with labeling as edited and attached to this review, and with the conditions for metrics and compliance as agreed upon with ODS and OC, under subpart H.
2. In addition to the package insert, blister pak and carton, all of the educational materials (patient, prescriber, pharmacy) and the patient voluntary survey are components of labeling and will require submission of a labeling supplement prior to change.
3. The voluntary survey should be instituted at time of initial roll-out.
4. The iPLEDGE system should be expanded to track movement of the product from wholesaler to pharmacy.

Jill Lindstrom, M.D.
Medical Officer/Dermatology

WITHHOLD 47 PAGE(S)

Draft Labeling

Medical Review

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

/s/

Jill Lindstrom
8/11/05 08:02:26 AM
MEDICAL OFFICER

Jonathan Wilkin
8/11/05 05:35:09 PM
MEDICAL OFFICER
I concur. Also, see Division Director Review Memorandum for additional comments.