# DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT FOR NDA 18-662

## ACCUTANE® (isotretinoin) CAPSULES

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# 1. EXECUTIVE SUMMARY

## 1.1 Background

Isotretinoin is a human teratogen that is uniquely efficacious for the treatment of severe recalcitrant, nodular acne in patients who are unresponsive to conventional therapy. The safe use of isotretinoin in women requires that every effort be made to 1) prevent pregnant women from taking isotretinoin; and 2) prevent women of childbearing potential from becoming pregnant 1 month before initiation of isotretinoin therapy, during therapy, and for 1 month after discontinuing isotretinoin treatment.

Isotretinoin was approved for use in the United States (US) in 1982 as Accutane, manufactured and marketed by Hoffmann-La Roche. Generic isotretinoin was introduced to the US market in November, 2002 (Table 1). Roche and the generic companies have the same risk management program for pregnancy prevention, however, this document focuses specifically on Roche's current Accutane risk management program for pregnancy prevention known as the System to Manage Accutane-Related Teratogenicity™ (S.M.A.R.T.™). The other companies' pregnancy prevention programs are representative of S.M.A.R.T. This document also summarizes a proposal for modifications to the current isotretinoin pregnancy prevention program.

**Table 1 Generic Companies and Their Isotretinoin Risk Management Programs for Pregnancy Prevention**

| Generic Isotretinoin | Manufacturer | Risk Management Program | Approval Date |
|---|---|---|---|
| Amnesteem | Mylan/Bertek[1] | S.P.I.R.I.T.[2] | November, 2002 |
| Sotret | Ranbaxy | I.M.P.A.R.T.[3] | December, 2002 |
| Claravis | Barr | A.L.E.R.T[4] | May, 2003 |

[1]Manufacturer: Genpharm.
[2]System to Prevent Isotretinoin-Related Issues and Teratogenicity.
[3]Isotretinoin Medication Program Alerting you to the Risks of Teratogenicity.
[4]Adverse Event Learning and Education Regarding Teratogenicity.

S.M.A.R.T. is highlighted by an intensive pregnancy prevention strategy that includes prescriber and patient educational components. S.M.A.R.T. requires two negative pregnancy tests prior to initiation of Accutane therapy, patient use of two forms of contraception simultaneously for 1 month before, during, and 1 month following Accutane treatment, and monthly pregnancy testing with a new written prescription for Accutane required each month following the negative pregnancy test. All patients are required to sign a general informed consent and female patients are required to sign a second, pregnancy-prevention informed consent. S.M.A.R.T. requires that all Accutane prescriptions have a properly-completed Accutane Qualification Sticker affixed to each prescription. The Qualification Sticker documents for a registered, dispensing pharmacy that a female patient has been qualified for Accutane therapy in accordance with the package insert and includes the date of qualification, patient gender, and directions regarding the cut-off date for filling the prescription (no more than 7 days after the patient qualification date). Thus, the Qualification Sticker is a surrogate marker for appropriate pregnancy testing and a patient's commitment to comply with the contraceptive requirements for Accutane use.

Two surveys are used to evaluate the effectiveness of the S.M.A.R.T. program: the Prescription Compliance and Accutane Surveys. The Prescription Compliance Survey assesses prescribers and dispensing pharmacists' appropriate use of the Accutane Qualification Sticker. The Accutane Survey assesses patient compliance with key elements of S.M.A.R.T. including pregnancy testing and contraceptive compliance. Each survey has several assessment metrics that were established by the FDA and Roche. An evaluation of the S.M.A.R.T. program to date, using data from each of these surveys, is provided.

The effectiveness of S.M.A.R.T. in reducing the number of Accutane-exposed pregnancies has also been examined. For this analysis, pregnancy data during S.M.A.R.T. (therapy start dates between April 1, 2002 to March 31, 2003) is provided along with a comparison to pregnancy data reported for the year prior to S.M.A.R.T. (therapy start dates between April 1, 2001 to March 31, 2002).

## 1.2 S.M.A.R.T. Evaluation

The main conclusions of the S.M.A.R.T. evaluation are as follows:

- S.M.A.R.T. has increased enrollment in the Accutane Survey, but the metric of having 60% enrollment of female patients within one year of S.M.A.R.T. initiation has not been met. Based on four demographic parameters, Accutane Survey participants are reasonably representative of all female Accutane users.
- Based on data from the Prescription Compliance Survey, Qualification Stickers are used and are used correctly for the vast majority (> 90%) of Accutane prescriptions. However, some women participating in the Accutane Survey did not recall two pre-prescription pregnancy tests before receipt of the initial Accutane prescription and did not use two forms of contraception simultaneously during treatment.
- S.M.A.R.T. has decreased the number of women who initiate Accutane therapy while pregnant. However, the absolute number of Accutane-exposed pregnancies has increased with S.M.A.R.T. The reasons for this are unclear, but two possible reasons are either 1) increased reporting because S.M.A.R.T. has increased public awareness; or 2) lack of contraceptive compliance. The reasons underlying contraceptive non-compliance are unclear and cannot be ascertained from the Accutane Survey in its current state.

## 1.3 Proposal for Isotretinoin Risk Management Program Enhancements

The proposal includes mandatory registration with a third party system of all prescribers of isotretinoin, all isotretinoin patients, and pharmacy registration for dispensing isotretinoin. It calls for separate risk management activities for females of childbearing potential, including pregnancy testing by an accredited laboratory, and regular interaction by all patients, prescribers, and pharmacists with the risk management system.

Key components of the program include the following:

- Mandatory prescriber registration.
- Mandatory registration of all patients, males and females.

- Mandatory registration of pharmacies.
- Prescriber attestation of patient education/qualification in the system for each isotretinoin prescription.
- Mandatory patient interaction with the educational and risk management evaluation component of the system.
- Mandatory reporting to the system of the results of a pregnancy test (for female patients of childbearing potential) conducted by an accredited laboratory within an appropriate time frame.
- Mandatory use of a Qualification Sticker on each isotretinoin prescription.
- Dispensing of isotretinoin to patient only if system authorizes it.
- Mandatory identification of product and amount dispensed.
- Centralized mechanism for reporting and follow-up of pregnancies.

## 2. ACCUTANE: BENEFIT/RISK

Severe recalcitrant nodular acne is a disfiguring disease in which deep inflammatory lesions can serve as portals for systemic bacterial infections and can often result in significant permanent scarring following healing. Pharmacological treatments for severe acne include broad-spectrum antibiotics. Antibiotics are efficacious in the treatment of severe acne because they reduce the inflammation associated with severe acne. However, since the mechanism of action of these medications does not mitigate the underlying etiology of the disease, many patients either need to remain on therapy for extended periods of time leading to increasing numbers of antibiotic-resistant bacteria on the skin or continue to have cysts and nodules that will likely lead to scarring.

Patients with severe recalcitrant nodular acne who have failed topical or systemic antibiotic treatment have few effective alternative therapeutic modalities. Accutane is an orally administered retinoid that is currently approved for the treatment of severe nodular acne in patients who are unresponsive (i.e., recalcitrant) to conventional therapy including topical treatments and systemic antibiotics. Accutane was approved in 1982 and thus, has been on the market for over 20 years. To date, over 6 million patients (approximately 50% female and 50% male) in the United States have been treated with Accutane.

A single course (0.5 to 2 mg/kg given in two divided doses daily for 15 to 20 weeks) of Accutane treatment has been shown to result in complete and prolonged remission of severe nodular acne in about 90% of cases [1, 2]. On average, Accutane treatment results in a 91% and 89% reduction in the number of lesions in males and females, respectively. Accutane treatment is also associated with a 80% reduction in nodule count in truncal acne, significantly reduces the total numbers of antibiotic-resistant bacteria on the skin of acne patients, and reduces the severity of scarring [3, 4, 5]. Currently, no efficacious alternative therapies to isotretinoin exist for these patients.

Accutane has also been used in treatment of pediatric neuroblastoma and multiple myeloma.

Isotretinoin manufactured by the other companies has been shown to be bioequivalent to Accutane.

Isotretinoin is a human teratogen. Thus, the safe and effective use of isotretinoin requires stringent precautions in treating severe recalcitrant nodular acne in women of childbearing potential. Female patients selected for isotretinoin treatment must not be pregnant for 1 month prior to initiating treatment and must not become pregnant during or for one month following treatment cessation.

Isotretinoin use is associated with other potentially serious adverse events including psychiatric disorders (depression, psychosis, and rarely suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors), pseudotumor cerebri, pancreatitis, hyperlipidemia, hearing impairment, hepatoxicity, inflammatory bowel disease, skeletal changes (bone mineral density changes, hypertosis, premature epiphyseal closure), and visual impairment (corneal opacities, decreased night vision). More frequent, less serious side effects include cheilitis, dry skin, skin fragility, pruritus, epistaxis, dry nose and dry mouth, and conjunctivitis.

Overall, the results from over twenty years of treatment experience with Accutane document a positive benefit/risk for isotretinoin therapy in the treatment of severe recalcitrant nodular acne.

# 3. EVOLUTION OF RISK MANAGEMENT INITIATIVES FOR PREGNANCY PREVENTION

Since Accutane's approval in 1982, Roche has worked with the FDA to assure that all prescribers and patients are aware that Accutane can cause birth defects and that every effort must be made to prevent pregnant women from taking Accutane and to prevent females of childbearing potential from becoming pregnant for 1 month before, during, and for one month after concluding treatment. Strategies to prevent maternal/fetal exposure to Accutane include both warnings in the product label and a risk management program for pregnancy prevention.

## 3.1 Accutane Package Insert for Pregnancy Prevention

Pregnancy labeling milestones for Accutane are summarized in Table 2. The current Accutane label is provided in Appendix page 59 .

Accutane was introduced to the US with a Category X pregnancy designation, the category designated for drugs that must be avoided under all circumstances during pregnancy. Warnings against any use of the product during pregnancy were contained in three sections of the package insert, WARNINGS, PRECAUTIONS, AND CONTRAINDICATIONS and in the patient information section. In addition, all Accutane-related materials provided to prescribers warned about the teratogenic potential of the drug.

The first report of a human malformation associated with Accutane exposure was received in June 1983 with additional reports of human malformations received within a month. Dear Doctor and Dear Pharmacist letters were sent out shortly thereafter to inform prescribers and pharmacists of the malformations and to reiterate the information from the CONTRAINDICATIONS section of the label regarding teratogenicity. Shortly thereafter, the PI was revised to move the pregnancy warnings in the

CONTRAINDICATIONS section of the label to a Black Box at the beginning of the insert. Subsequent changes to the Black Box have included the following: 1) insertion of an avoid pregnancy logo; 2) inclusion of information about the types of human malformations reported; and 3) requirements for pregnancy testing.

**Table 2 Accutane Pregnancy Labeling Milestones**

| Date | Action |
|---|---|
| June 1982 | US approval with pregnancy contraindication. |
| August 1983 | Bold print pregnancy warnings in Contraindications, Warnings, and Precautions sections. |
| February 1984 | Black Box pregnancy warnings added. |
| August 1988 | Avoid pregnancy logo inserted. |
| October 1988 | Pregnancy Prevention Program initiated. |
| April 1990 | Birth defects information included in Black Box. |
| December 1993 | Need for pregnancy testing added to Black Box. |
| May 2000 | Language about pregnancy testing modified.<br>Accutane Medication Guide distributed with the Accutane BlisterPak™.<br>Required female patients to view a non-branded videotape on contraception. |
| October 2001 | Pregnancy test of at least 25 mIU β-HCG required. |
| January 2002 | System to Manage Accutane Related Teratogenicity™ initiated. |
| August 2003 | *Be Aware, The Risks of Pregnancy While on Accutane* video added. |

## 3.2 Risk Management Program for Pregnancy Prevention

In addition to pregnancy labeling, the first risk management program for pregnancy prevention was implemented by Roche in October 1988. Since inception, the risk management goals of the program have been to ensure that no one begins Accutane therapy if pregnant and no pregnancies occur while on Accutane therapy. The risk management program for pregnancy prevention was known as the Pregnancy Prevention Program (PPP) from 1988 through the end of 2001. A new program, the System to Manage Accutane-Related Teratogenicity™ (S.M.A.R.T.™ ), was initiated with a transition period in January 2002 and became mandatory in April 2002. The primary focus of this submission is the S.M.A.R.T. program; however, to understand the evolution of S.M.A.R.T., information on the PPP is also provided.

### 3.2.1 Pregnancy Prevention Program

#### *3.2.1.1 Program Overview*

In 1988, Roche introduced the PPP to try to further reduce the risk of maternal/fetal exposure to Accutane. The PPP was designed to communicate to both patients and prescribers information about the teratogenicity of Accutane and preventive strategies for maintenance of a non-pregnant state for 1 month before, during, and for 1 month following Accutane treatment. The PPP was the first risk management program introduced by a pharmaceutical company. Components of the program were as follows:

- PI modified to require a negative pregnancy test within one week before starting Accutane and to recommend monthly pregnancy testing and contraceptive counseling. Referrals and reimbursement for contraceptive counseling are provided by Roche.
- PI modified to require two forms of effective contraception simultaneously for 1 month before, during, and 1 month following Accutane therapy.
- Blister packaging that includes an avoid pregnancy symbol and text emphasizing the need to avoid taking Accutane if pregnant, the need to maintain a non-pregnant state for 1 month before, during, and 1 month following Accutane treatment by using two effective forms of contraception.
- Educational materials to help prescribers counsel patients about contraceptives and pregnancy avoidance (Section 3.3).
- Female patient informed consent.
- Methods to evaluate the effectiveness of the PPP at modifying prescriber and patient behaviors (Section 3.2.1.2).

#### *3.2.1.2 Methods to Evaluate PPP Effectiveness*

Two methods were used to evaluate the effectiveness of the PPP: the Accutane Prescriber Tracking Survey and the Accutane Survey.

The Accutane Prescriber Tracking Survey was a telephone interview survey of dermatologists and primary care physicians who had prescribed Accutane at least once during a 12-month period. The purpose of the Prescriber Tracking Survey was to determine the usage of the individual elements of the PPP by prescribers.

The PPP Accutane Survey was a voluntary written or telephone questionnaire given to patients at various timepoints during Accutane treatment. The Survey was developed by the Slone Epidemiology Center (SEC) at Boston University and implemented in 1989. The objectives of the PPP Accutane Survey were to determine the following:

1. The rate of pregnancy among female Accutane users.
2. Patient awareness of the teratogenic risks of Accutane.
3. History of prior acne therapy.
4. Pregnancy outcome among users who become pregnant.
5. Risk factors for the occurrence of pregnancy.
6. Impact of an intensive survey on compliance with prescribing guidelines.

#### *3.2.1.3 Pregnancy Reporting Requirements*

Since 1989, Roche has been required to submit to the Agency, Accutane Quarterly Information Reports that contain a tabular listing of all serious adverse event cases from both US and non-US sources and the following pregnancy information:

- A summary of the total number of US maternal-fetal exposed cases by year of therapy and pregnancy class or outcome.
- A summary of the total number of US maternal-fetal exposed cases resulting in congenital malformation presented by year of birth or by pregnancy outcome.

- All initial US pregnancy cases reported during the quarter period (maternal-fetal exposed).
- All US pregnancy cases where additional follow-up information has been received during the quarter period for cases that had previously been reported in an Accutane Quarterly Information Report.
- A section for all US and non-US pregnancy cases resulting in congenital malformation (initial cases only) by source of report and by country.

In addition, Roche submits to the Agency annual periodic safety reports that contain the following pregnancy information:

- All pregnancy exposures, regardless of outcome or adverse event labeling, as serious, labeled event reports.
- A summary and discussion of the clinical significance of the pregnancy exposures.

Furthermore, effective October 2000, all US and non-US maternal-fetal exposed cases of congenital malformations are submitted as 15-day expedited reports.

## 3.3 Additional Pregnancy Prevention Activities

In addition to the PPP, the following pregnancy prevention activities have been also carried out by Roche:

- Voluntary Continuing Medical Education and Continuing Education offerings for physicians, nurse practioners, and registered nurses working in the fields of dermatology and reproductive health.
- Roche Pharmaceuticals Service Center: provides healthcare professionals with verbal and written medical responses to unsolicited medical queries.
- Toll-free number for Accutane information provided in the 13 most common languages spoken in the United States.
- Toll-free, confidential, 24-hour, contraceptive information line.
- Reimbursement for a contraception counseling referral.
- Accutane Patient Medication Guide which is contained and dispensed with each Accutane BlisterPak™.
- *Be Prepared, Be Protected*, a non-branded video that provides five scenarios about women who are having difficulty complying with pregnancy avoidance followed by comments from a counselor who provides solutions for each scenario.

These pregnancy prevention activities were continued with S.M.A.R.T. and will continue with the proposed program (Section 8).

# 4. ENHANCED PREGNANCY PREVENTION PROGRAM: S.M.A.R.T.

The current Accutane risk management program for pregnancy prevention, S.M.A.R.T., is the result of efforts to enhance the Accutane PPP and is based in part on data generated from the PPP Accutane Survey. The PPP was the subject of a Dermatologic and Opthalmic Drugs Advisory Committee in 2000. Following this Advisory Committee, Roche developed and submitted to the Agency on March 26, 2001, two proposals aimed

at further reducing the risk of Accutane-exposed pregnancies: 1) a prescriber and patient registry; and 2) a program that provided a link between a negative pregnancy test and the dispensing of Accutane via an Accutane Qualification Sticker. A number of subsequent discussions with the Agency about these two proposals ensued. During these discussions, critical issues regarding a prescriber and patient registry including continuing to make Accutane available without extraordinary burdens on patients and precribers and maintaining patient rights and patient confidentiality were raised by both sides. The Agency clarified that their critical concern was the link between the dispensing of Accutane and a negative pregnancy test. Following these discussions, the alternative program to a registry, S.M.A.R.T., was approved by the Agency on October 30, 2001 (Appendix page 97) with the requirement that the adequacy of S.M.A.R.T. be re-evaluated one year after implementation and that Roche develop a back-up program that included the following: 1) mandatory registration of both males and females receiving Accutane; 2) mandatory registration of practitioners prescribing Accutane; 3) mandatory reporting of all fetal exposures to Accutane; and 4) mandatory restricted distribution through registered pharmacies.

S.M.A.R.T. was initiated with a transition period in January 2002 with information distributed to physicians, nurses, and pharmacists and became mandatory on April 10, 2002. The additional pregnancy prevention activities detailed in Section 3.3 were continued with S.M.A.R.T. The remainder of this document reviews elements of the S.M.A.R.T. program, evaluates the effectiveness of S.M.A.R.T., and recommends modifications to S.M.A.R.T.

## 4.1 Program Overview

As shown in Table 3, many elements of the PPP have been preserved with S.M.A.R.T. such as requiring that patients use two safe and effective forms of contraception for 1 month before, during, and 1 month following Accutane therapy. However, there are two key differences between S.M.A.R.T. and the PPP: 1) the Prescriber *Letter of Understanding* (Appendix page 103); and 2) the requirement that a prescriber affix an Accutane Qualification Sticker (Appendix page 102) to each 30-day prescription for Accutane that documents for the dispensing pharmacist that the prescriber has qualified the patient according to the qualification criteria in the CONTRAINDICATIONS AND WARNINGS section of the PI (Appendix page 59).

Key elements of S.M.A.R.T are as follows:

- To prescribe Accutane, the prescriber must obtain a supply of yellow self-adhesive Accutane Qualification Stickers. Prior to obtaining these stickers, the prescriber has to register with a database of Accutane prescribers by reading the booklet entitled *System to Manage Accutane-Related Teratogenicity, Guide to Best Practices* and signing and returning the completed S.M.A.R.T. *Letter of Understanding*.
- Accutane should not be prescribed or dispensed to any patient (male or female) without a properly completed yellow self-adhesive Accutane Qualification Sticker attached to each Accutane prescription.
- For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies 1) that she has had negative urine or serum pregnancy tests as described in the PI;

2) has selected and committed to use two forms of effective contraception simultaneously, as described in the PI; 3) has signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin; and 4) has been informed of the purpose and importance of participating in the Accutane Survey and been given the opportunity to enroll.

- The yellow self-adhesive Accutane Qualification Sticker documents that the female patient is qualified, and includes the date of qualification, patient gender, directions regarding the cut-off date for filling the prescription (within 7 days after patient qualification), and up to a 30-day supply limit with no refills.
- Pharmacists may dispense Accutane only on receiving a written prescription with the Accutane Qualification Sticker that has been appropriately completed. Refills require a new prescription with a yellow self-adhesive Accutane Qualification Sticker. No telephone or computerized prescriptions are permitted. An Accutane Medication Guide must be given to the patient each time Accutane is dispensed and is supplied in each Accutane BlisterPak™.

The S.M.A.R.T. PI requirements described above are reinforced by focused educational materials. Metrics for evaluating the success of S.M.A.R.T. were jointly determined by Roche and the FDA. Elements of S.M.A.R.T. including the prescriber, pharmacist, and patient requirements are described in detail in Section 4.2. Metrics used to evaluate the effectiveness of the S.M.A.R.T. program and the corresponding results are described in Sections 4.3, 5, and 6, respectively.

**Table 3 A Comparison of the PPP and S.M.A.R.T.**

| Program Features | PPP | S.M.A.R.T |
|---|---|---|
| Registration of Prescriber | | X |
| Educational Component: | | |
| Educational Booklets | X | X |
| Patient Informed Consent | X | X |
| Medication Guide | X | X |
| Videos | X | X |
| Authorized Prescriber Check Mechanism | | X |
| Link of Pregnancy Test to Dispensing | | Via Accutane Qualification Sticker |
| Limited to 30 Days Supply/No Refills | | X |
| Special Packaging | X | X |
| Use of Qualification Sticker | | X |
| Auditing Mechanism | | X |
| Contraceptive Counseling | X | X |

## 4.2 S.M.A.R.T. Requirements

S.M.A.R.T. has specific requirements that target all aspects of the Accutane prescribing chain including prescribers, dispensing pharmacists, and patients.

### 4.2.1 Prescriber Requirements

Three components of S.M.A.R.T. target prescribers:

1. An educational booklet entitled, *S.M.A.R.T. Guide to Best Practices*.
2. A *S.M.A.R.T. Letter of Understanding*.

3. A yellow self-adhesive Accutane Qualification Sticker to be completed and affixed to an Accutane prescription.

The *S.M.A.R.T. Guide to Best Practices* includes information about the following: 1) Accutane's teratogenic potential; 2) pregnancy testing; 3) effective contraception and the limitations of contraceptive methods; 4) behaviors associated with an increased risk of contraceptive failure and pregnancy; 5) methods to evaluate pregnancy risk; and 6) method to properly complete a qualified Accutane prescription.

The *S.M.A.R.T. Letter of Understanding* attests that Accutane prescribers understand that Accutane is a human teratogen, have read the *S.M.A.R.T. Guide to Best Practices,* and understand their responsibilities to minimize the risk of fetal exposure to Accutane including monthly pregnancy avoidance counseling and pregnancy testing, and understand how to qualify female patients for an Accutane prescription.

The yellow self-adhesive Accutane Qualification Stickers can only be obtained by prescribers after signing and returning the *S.M.A.R.T. Letter of Understanding* and thus, registering with the prescriber database. By signing and returning the *S.M.A.R.T. Letter of Understanding*, a prescriber affirms the following:

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

Prescribers confirm that a female patient of childbearing potential has been qualified as described in the CONTRAINDICATIONS AND WARNINGS section of the PI by attaching a self-adhesive Accutane Qualification Sticker to the prescription.

Additional pregnancy prevention activities directed at prescribers include a toll-free number for professional support, professional continuing education, and distribution of urine pregnancy tests (Section 3.3).

### 4.2.2 Pharmacist Requirements

Before dispensing each Accutane prescription, the pharmacist must note the following:

- Presence of a properly-completed Accutane Qualification Sticker affixed to an Accutane prescription. This Sticker documents for the dispensing pharmacist that a

female patient has had negative urine or serum pregnancy tests as described in the PI and has selected and committed to use two forms of effective contraception simultaneously, as described in the PI.
- Prescriptions for all patients are not filled more than 7 days after patient qualification.
- Prescription is written for no more than a 30-day supply and there are no automatic refills. Telephone- or computer-generated prescriptions are not permitted.
- The Accutane Medication Guide is dispensed with each prescription.

In addition, the pharmacist can verify that the prescriber is registered in the prescriber database.

Beginning in October 2002, a Medication Guide was included in each Accutane BlisterPak™. Prior to this, the pharmacist gave the Accutane Medication Guide to each patient at the time of dispensing. Roche implemented an Accutane exchange program at that time to expedite the distribution of the new Accutane packages with the Medication Guide, thus minimizing the Medication Guide distribution burden on pharmacists and reducing the potential risk of patients not receiving a Medication Guide with each Accutane prescription.

### 4.2.3 Female Patient Requirements

To prevent women from starting Accutane while pregnant and becoming pregnant while taking Accutane, the S.M.A.R.T. program necessitates ascertainment of a non-pregnant state with the dispensing of each Accutane prescription. Female patient requirements for the S.M.A.R.T. program are as follows:

- Must have two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL β-HCG before receiving the initial Accutane prescription. The first test is a screening test obtained by the prescriber when the decision is made to pursue qualification of a female patient for Accutane. The second test is a confirmatory test that is to be performed during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For each month of Accutane therapy, the patient must have a negative result from either a urine or serum pregnancy test before receiving the next Accutane prescription. Roche makes available urine pregnancy test kits for the screening, confirmatory, and monthly pregnancy tests. There is no requirement that any of these tests be medically confirmed.
- Must select and commit to use two forms of effective contraception simultaneously for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month following discontinuation of Accutane therapy. At least one form of contraception has to be a primary form. Primary forms of contraception include tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, or topical/injectable/implantable/insertable hormonal birth control products, unless abstinence is the chosen method or the patient has undergone a hysterectomy. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps, each of which is to be used with a spermicide.
- Must sign a patient information/consent form that contains warnings about potential birth defects if a fetus is exposed to isotretinoin, and

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

The importance of avoiding pregnancy while receiving Accutane treatment is reinforced by a patient educational booklet entitled *Be Smart*, *Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women* which is designed to be reviewed in detail by the prescriber with each female patient. This booklet contains information about contraceptive compliance, an Accutane Survey enrollment form, an informed consent form that helps to document that the patient understands the risks of treatment with Accutane, a separate informed consent form that documents that the patient understands the teratogenic risk of treatment with Accutane, the need to avoid pregnancy, and her responsibilities before, during, and after therapy, and a patient qualification form for pregnancy prevention and contraceptive compliance that confirms that a female patient has met the following four qualification criteria as outlined in the CONTRAINDICATIONS AND WARNINGS section of the PI:

1. I am required to have two negative pregnancy tests showing that I am not pregnant before my prescriber can prescribe Accutane. I agree to schedule regular monthly appointments throughout my therapy for pregnancy tests and for other tests to monitor my body's response to Accutane. It is important to my health and well-being to keep every scheduled appointment faithfully.
2. I am aware of the effects that Accutane may have on my unborn baby if I become pregnant during treatment and for 1 month following treatment. I have selected as my primary contraception method: (*patient to specify*) and secondary contraception method (*patient to specify)*. I will use both of these methods at the same time while on therapy and for 1 month afterward.
3. My prescriber has given both oral and written warnings of the hazards of taking Accutane during pregnancy (exposing the fetus to the drug) and I have signed the Patient Information/Consent Form.
4. I have been given the opportunity to participate in the Accutane Survey.

Additional educational reinforcement components available to female patients (Section 3.3) include Preventing Pregnancy – A Guide to Contraception, a section in *Be Smart*, *Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women*, referrals and reimbursement for contraceptive counseling, a toll-free Accutane information line, the Accutane Medication Guide supplied with each Accutane prescription, and blister packaging that includes an avoid pregnancy symbol and text emphasizing the need to avoid taking Accutane if pregnant, and the need to maintain a non-pregnant state for 1 month before, during, and 1 month following Accutane treatment by using two effective forms of contraception simultaneously.

## 4.3 Methods to Evaluate S.M.A.R.T. Effectiveness

The effectiveness of the S.M.A.R.T. program during its first year was evaluated using the following:

- The Prescription Compliance Survey.
- A S.M.A.R.T.-revised Accutane Survey.

- Pregnancy case reports for a time period before S.M.A.R.T. (therapy start dates April 1, 2001 to March 31, 2002) versus during S.M.A.R.T. (therapy start dates April 1, 2002 to March 31, 2003) with the report received by August 15, 2002 and August 15, 2003, respectively.

The Prescription Compliance Survey is designed to evaluate compliance with the Accutane Qualification Sticker. The Accutane Survey is designed to evaluate compliance with key elements of the S.M.A.R.T. program and to ascertain patient knowledge of Accutane-related teratogenicity and the rate of occurrence of Accutane-exposed pregnancies. Each Survey has assessment metrics that were jointly agreed upon by Roche and the FDA. As part of S.M.A.R.T. approval, Roche was required to submit to the Agency a comprehensive report on the S.M.A.R.T. program, including information on the metrics achieved during the first full one year of implementation of the Accutane Qualification Stickers. An additional report is required after two years of implementation of the Accutane Qualification Stickers.

### 4.3.1 Prescription Compliance Survey

The goal of the Prescription Compliance Survey is to assess prescribers' and dispensing pharmacists' compliance with the use of the Accutane Qualification Sticker, a key component of the S.M.A.R.T. program.

The following assessment metrics were established for the Prescription Compliance Survey:

- 90% of all prescribers will use the Accutane Qualification Stickers by one year after labeling change and close to 100% by two years after labeling change.
- 90% of all prescribers completely and correctly complete the Accutane Qualification Sticker by one year after labeling change and close to 100% by two years after labeling change.
- 90% of all prescriptions are dispensed with a Medication Guide by one year after labeling change and close to 100% by two years after labeling change. To achieve this metric, a Medication Guide was included with each BlisterPak™ of Accutane tablets in October 2002.

To assess use of the Accutane Qualification Sticker, a retrospective quarterly survey of a random sample of US retail pharmacies was conducted in which pharmacists were asked to complete a questionnaire pertaining to Accutane prescriptions that had been dispensed during the preceding month. The survey was planned to be conducted using eight independent samples of 750 pharmacies (total of 6,000 pharmacies sampled) each surveyed on a quarterly basis for 24 months. The eight pharmacy samples were independently drawn from the national SK&A pharmacy database that includes all retail pharmacies located in the 48 continental United States. The survey does not measure compliance with S.M.A.R.T. for those prescriptions filled by mail order. A repeated random sampling methodology was applied to prevent a pharmacy from responding more than once, thus reducing selection bias. Survey results from each quarterly period are referred to as first survey wave, second survey wave, etc. Results for five survey waves are currently available. During the third wave of the survey, five pharmacy chains

requested that their stores not be included in the Survey: Walmart, Walgreen's, Eckerd, CVS, and Rite-Aid. The removal of these five chains reduced the population of pharmacies from which samples can be taken by 31% (15,289 pharmacies).

To assure validity of the collected data, responding pharmacists were not told that the main objective of the study was to assess the presence of the Qualification Sticker on Accutane prescriptions. The survey is retrospective since pharmacists are asked to report on the use of the Qualification Sticker for Accutane prescriptions that have already been dispensed.

To complete the Prescription Compliance questionnaire, pharmacists were asked to reference original paper prescriptions written for Accutane to answer questions regarding the presence of the Qualification Sticker and whether or not the Sticker was appropriately completed. Additional data regarding how the prescription was written (drug name used, manufacturer, strength, authorized refills, mode of receipt) and whether or not the Accutane Medication Guide was dispensed (until the Medication Guide was included with the Accutane BlisterPak™) were recorded. Patient characteristics (gender, age, payment method) and pharmacy characteristics (geographic region, urban/rural location, and store size [independent/small chain, large chain]) were also recorded.

To ensure the validity of the data obtained by the questionnaires, a random sample of 15% of the responding pharmacies for each of the first four waves of the Survey were recruited to photocopy the original Accutane prescriptions they were using for reporting and submit these copies via mail or facsimile to the study data processing center. The photocopied prescriptions were compared with the corresponding questionnaire responses to determine the completeness and accuracy of the reported data. Patient personal identifiers were removed by the pharmacist from these documents prior to their photocopying.

### 4.3.2 Accutane Survey

With the advent of the S.M.A.R.T. Program, the Accutane Survey (Appendix page 105) was revised to better reflect S.M.A.R.T. program strategies and objectives. The overall goal of the revised Accutane Survey is to assess compliance with S.M.A.R.T. Specific objectives of the S.M.A.R.T. Accutane Survey are as follows:

1. To determine female patient awareness of the teratogenic risks of Accutane.
2. To measure compliance with key elements of S.M.A.R.T., including patient informed consent, pregnancy testing, contraception use, Medication Guide, and Accutane Qualification Stickers.
3. To calculate the rate of pregnancy among female Accutane users.
4. To identify risk factors for the occurrence of pregnancy.

Women can enroll in the S.M.A.R.T. Accutane Survey using an enrollment form provided in the Accutane BlisterPak™, an enrollment form provided in the patient educational booklet, *Be Smart, Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women*, or through a toll-free number. However, for S.M.A.R.T., emphasis is placed on having the patient enroll in the Survey at a prescriber

visit when the prescriber and patient are reviewing the booklet, *Be Smart*, *Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women*.

Once enrolled in the Survey, written questionnaires are sent to patients at various timepoints during Accutane treatment. For 80% of enrollees, information is sought at specific time points during Accutane treatment; for the remaining 20% information is sought only after completion of treatment. The questionnaires contain multiple questions that inquire about behaviors and knowledge relevant to pregnancy prevention during Accutane treatment. Specifically, data is collected about patient use of two methods of contraception, patient recall of two pregnancy tests prior to receiving the initial Accutane prescription, patient recall of the yellow Qualification Sticker on the prescription, and patient recall of pregnancy testing and dispensing of the prescription within the required timeframes. There are also questions that inquire about the patient's knowledge of the various Accutane Survey enrollment methods and why a particular enrollment method was chosen. Several questions inquire about sexual activity, contraceptive practices, and the occurrence of pregnancy. Specific questions are also asked about whether a patient was taking Accutane or a generic brand of isotretinoin.

To identify the occurrence of Accutane-exposed pregnancies, follow-up continues for all women until at least six months have elapsed since completion of Accutane treatment; this interval approximates the first two trimesters of pregnancy by which time all Accutane-exposed pregnancies are likely to have come to attention. This amounts to approximately 11 months of follow-up for each Survey enrollee. All patients are monetarily compensated for Survey participation.

For approximately the first 7 months of the S.M.A.R.T. Program (April 2002 to November 2002), the Accutane Survey was conducted by the SEC, who did not implement the S.M.A.R.T.-revised Survey. During the third Quarter of 2002, responsibility for conduct of the Survey was transferred from the SEC to S.I. International who implemented the S.M.A.R.T.-revised Survey; analysis of the data was undertaken by its subcontractor, The Degge Group, Ltd. The transition from SEC to SI/Degge is expected to be complete in January 2004.

The differences between the Accutane Surveys implemented by the two vendors are minimal and are concerned primarily with compliance with specific S.M.A.R.T. enhancements (e.g., Accutane Qualification Sticker, two pregnancy tests before initial prescription, etc.), added to the pregnancy prevention program. The Accutane Survey administered by SEC does not query patients about compliance with S.M.A.R.T.-specific requirements, whereas the survey administered by SI/Degge does. The SI/Degge Survey also asks patients which isotretinoin they are taking. For SI/Degge analyses, patients who report receiving any Accutane or a combination of generic isotretinoin and Accutane or who don't know are considered to have taken Accutane; those who indicate they have only taken generic isotretinoin are excluded from the Accutane Survey analyses. For the SEC data, there is no way to determine whether a patient was using generic or branded isotretinoin; thus, all patients were included in SEC analyses of Survey data. Because of the differences between the Survey data for the two vendors, summary tables of Accutane Survey data note the data source as either the SEC or SI/Degge.

The following assessment metrics were established by Roche and the FDA for the Accutane Survey:

- 60% of female Accutane patients enrolled in the Survey one year after implementation of S.M.A.R.T. to reduce the likelihood of sample selection bias.
- Assessment of the representativeness of Survey participants relative to female Accutane patients to determine whether or not the Survey is biased.
- Percentage of patients with recall of taking a pregnancy test.
- Percentage of patients with recall of the Qualification Sticker affixed to their Accutane prescription.
- Percentage of patients with recall of receiving a Medication Guide. This metric has been achieved by inclusion of a Medication Guide with each BlisterPak™ of Accutane tablets. Thus, no information for this metric is supplied in this document.
- Percentage of patients with recall of using two forms of safe and effective contraception.
- Percentage of patients enrolling in the Accutane Survey via the prescriber's office, Accutane BlisterPak™, and by toll-free number.

### 4.3.3 Pregnancy Reporting

Every incoming pregnancy case, whether it is received spontaneously or from the Accutane Survey or other special study, undergoes a preliminary duplicate search by the Roche Drug Safety triage coordinator. Known demographics, such as birth date, initials, state, etc., are fields that are routinely checked by the triage coordinator. After the case is processed and sent to Roche Drug Safety Central Operations, another duplicate search is performed, where additional fields can be checked (e.g., last menstrual period). In the event that a duplicate is found at a later date, the cases are merged.

For this report, pregnancy cases have been classified according to Accutane treatment initiation and reporting dates. The case classification is follows:

- Pre-S.M.A.R.T.
  1. Cases reported April 1, 2001 - August 15, 2002 with treatment initiation date known to be April 1, 2001 - March 31, 2002.
  2. Cases reported April 1, 2001 - March 31, 2002 treatment initiation dates unknown.
- S.M.A.R.T.
  1. Cases reported April 1, 2002 - August 15, 2003 treatment initiation dates known to be April 1, 2002 - March 31, 2003.
  2. Cases reported April 1, 2002 - March 31, 2003 treatment initiation dates unknown.

# 5. RESULTS: S.M.A.R.T. PRESCRIBERS AND ACCUTANE SURVEY PARTICIPANTS

## 5.1 Prescribers

The prescriber *Letter of Understanding* must be completed and returned to Roche in order for a prescriber to receive a supply of Accutane Qualification Stickers for use on his/her prescriptions for Accutane. Completion of the form signifies an awareness by prescribers of the safe and effective use of Accutane as described in the PI.

As of May 23, 2003, 25,102 prescribers have completed and returned a *Letter of Understanding* to Roche. Of these, the majority are dermatologists and family practitioners (Table 4).

**Table 4 Prescriber Uptake of Letter of Understanding, January 2, 2002 – May 23, 2003**

| Specialty | Number of Prescribers | Percent of Total* |
|---|---|---|
| Dermatology | 12,476 | 49.7% |
| Family Practice | 7,045 | 28.1% |
| Internal Medicine | 1,547 | 6.2% |
| Pediatrics | 706 | 2.8% |
| Family Medicine | 559 | 2.2% |
| General Practice | 371 | 1.5% |
| Hematology/Oncology | 340 | 1.4% |
| Pediatric Heme/Onc | 272 | 1.1% |
| OB/GYN | 170 | 0.7% |
| General Medicine | 131 | 0.5% |
| Other | 689 | 2.7% |
| Unknown | 796 | 3.2% |
| **Total** | **25,102** | **100.0%** |

*Percentage based on the total number of prescribers who completed and returned the *Prescriber Letter of Understanding*.

## 5.2 Accutane Survey

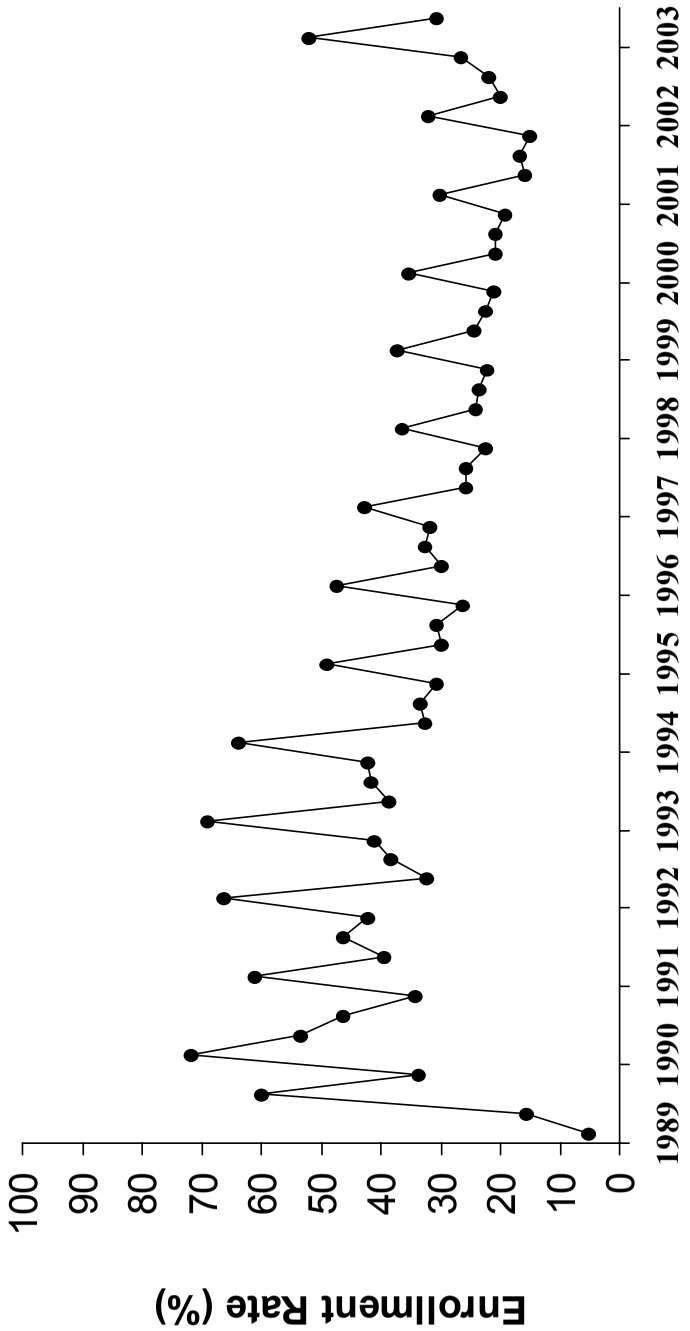
Enrollment in the Accutane Survey is voluntary and thus, the Survey does not enroll every woman who uses Accutane. Without universal enrollment in the Survey, there is no way to insure that enrolled patients are comparable to patients who do not enroll,

raising the concern that women who participate in the Survey may be at a lower risk for pregnancy because of a higher level of compliance with S.M.A.R.T. To minimize the likelihood of biased sample selection, the goal of S.M.A.R.T. was to increase Accutane Survey enrollment to 60% within one year of implementation by encouraging patients to enroll at a prescriber visit.

### 5.2.1 Enrollment Rate

The Accutane Survey achieved an overall enrollment rate of 28.2% for the first year of the S.M.A.R.T. program compared to approximately 17% for the year prior to S.M.A.R.T. Survey enrollment increased substantially in the first four quarters of S.M.A.R.T. compared with the four quarters prior to S.M.A.R.T. (Figure 1). This reverses a downward trend in Accutane Survey enrollment rates (Figure 1), but falls short of the metric of 60% enrollment of female patients in the Survey. The elevated enrollment rate (52%) for the fourth quarter of S.M.A.R.T. (i.e., the first quarter of the calendar year 2003) followed by a decline in the fifth quarter of S.M.A.R.T. is consistent with a pattern of elevated enrollment rates in the first quarter of the calendar year that is evident throughout the Survey's history (Figure 1). It is not clear whether this represents a measurement artifact or some other phenomenon.

Figure 1 Accutane Survey Quarterly Enrollment Rates, 1989-June 30, 2003



### 5.2.2 Methods of Enrollment

One goal of the S.M.A.R.T. Program was to encourage patient enrollment in the Accutane Survey while in the prescriber's office. During the course of the first year of S.M.A.R.T., the percentage of patients enrolling at the prescriber's office more than doubled from the years prior to S.M.A.R.T. (Table 5).

**Table 5 Methods of Accutane Survey Enrollment**

| | S.M.A.R.T. | Pre-S.M.A.R.T. |
|---|---|---|
| **Enrollment Method** | | |
| Doctor | 56% | 21% |
| BlisterPak™ | 43% | 76% |
| Telephone | 1% | 3% |

### 5.2.3 Representativeness of Survey Participants

Accutane Survey participants were compared to a reference population for four demographic parameters: 1) age; 2) region of residence in the US (East, Midwest, South, and West); 3) payer type (cash, Medicaid, third party); and 4) prescriber (dermatologist, non-dermatologist). For the reference population, these parameters were calculated using annualized data for the time period of April 1, 2002 to March 31, 2003 and marketing information.

Accutane Survey participants were similar to the Accutane female population with respect to age and geographic region (Table 6). Cash-paying patients and patients receiving their prescriptions from dermatologists were over-represented in the Survey compared to the reference population (Table 6).

**Table 6 Comparison of Accutane Survey Participants to the Female Accutane Population**

| Parameter | Accutane Survey Participants | Female Accutane Population |
|---|---|---|
| **Age group**[1] | N=36331 | N=194,397 |
| 0-11 | 41 (0.1%) | 1,329 (0.7%) |
| 12-15 | 4498 (12.4%) | 32,312 (16.6%) |
| 16-19 | 9233 (25.4%) | 46,506 (23.9%) |
| 20-29 | 13211 (36.4%) | 48,329 (24.9%) |
| 30-39 | 6460 (17.8%) | 32,745 (16.8%) |
| 40-44 | 1746 (4.8%) | 12,026 (6.2%) |
| 45+ | | 21,150 (10.9%) |
| | | |
| **Geographic region**[2] | N=36535 | N=466,504 female prescriptions |
| East | 5770 (15.8%) | 98835 (21.2%) |
| Midwest | 8366 (22.8%) | 95453 (20.5%) |
| South | 12434 (34.0%) | 163691 (35.1%) |
| West | 9965 (27.3%) | 108525 (23.3%) |
| | | |
| **Payer**[3] | N=456 | N=1,033,580 female prescriptions |
| Cash | 50 (11%) | 82,032 (8%) |
| Medicaid | 12 (3%) | 15,922 (2%) |
| Third party | 338 (74%) | 935,896 (91%) |
| Unknown | 56 (12%) | - |
| | | |
| **Prescriber**[3] | **N=5447** | **N=1,030,209 female prescriptions** |
| Dermatologist | 5124 (94.1%) | 787,276 (76.4%) |
| Non-dermatologist | 300 (5.5%) | 200,515 (19.5%) |
| Unknown | 23 (<1%) | 42,148 (4.1%) |

[1]Data source: Accutane Survey enrollment forms and NDC health.
[2]Data source: Accutane Survey enrollment forms and IMS.
[3]Data source: Accutane Survey DAT2 questionnaire and IMS.

## 5.3 Conclusions

S.M.A.R.T. efforts to increase enrollment in the Accutane Survey have reversed a historical downward trend in enrollment rates, but still fall short of enrolling 60% of female patients. Survey participants are reasonably representative of all female Accutane users. However, given the voluntary nature of the Survey and the lack of 100% participation, there is no way to definitively conclude that non-participants aren't different from those who enroll and ultimately respond.

# 6. RESULTS: COMPLIANCE WITH S.M.A.R.T. RISK MANAGEMENT ACTIVITIES

## 6.1 Pregnancy Testing

S.M.A.R.T. requires that all female patients have two negative pregnancy tests before receiving the initial Accutane prescription and a negative pregnancy test for each subsequent month of Accutane therapy. The Accutane Qualification Sticker attached to the written prescription signifies that a female patient has had negative urine or serum

pregnancy tests as described in the PI. Thus, utilization of the Qualification Sticker is a surrogate marker for appropriate pregnancy testing. Compliance with the Accutane Qualification Sticker was assessed using the Prescription Compliance and Accutane Surveys. Patient recall of pregnancy testing was assessed using the Accutane Survey.

### 6.1.1 Accutane Qualification Sticker

During the first five waves of the Prescription Compliance Survey, greater than 90% of dispensed Accutane prescriptions had a Qualification Sticker attached and correctly completed (Table 7). A similar percentage of Accutane Survey respondents (97%) recall that a Qualification Sticker was affixed to their prescription (Table 8).

The Prescription Compliance Survey also found that urban pharmacies were more likely to dispense complete Accutane prescriptions than rural pharmacies (Table 9). A low percentage of the audited prescription records (approximately 5%; 24/472) did not match the original survey data.

**Table 7 Use of Accutane Qualification Sticker – Prescription Compliance Survey**

| | Survey Wave | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Qualification Sticker affixed, % | 95.9 | 97.1 | 97.6 | 98.5 | 98.9 |
| Lower, upper bound, % | 93.4, 97.8 | 94.8, 98.6 | 95.6, 98.9 | 96.2, 99.7 | 96.6, 99.9 |
| Qualification Sticker correctly completed, % | 94.1 | 97.7 | 96.9 | 97.5 | 96.1 |
| Lower, upper bound, % | 91.1, 96.4 | 95.5, 99.0 | 94.6, 98.5 | 94.7, 99.1 | 92.6, 98.3 |

**Table 8 Patient Recall of Qualification Sticker – Accutane Survey**

Source: DAT1, Degge/S.I. only; DAT1's returned as of August 15, 2002

| | Total under S.M.A.R.T. N=5395 |
|---|---|
| | n(%) |
| Accutane Qualification Sticker received with prescription | 4950 (97%) |

**Table 9 Qualification Sticker Completeness by Pharmacy Population Density - Prescription Compliance Survey**

| | Survey Wave | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| **Urban** | | | | | |
| Percentage complete | 97.2 | 99.1 | 99.6 | 99.4 | 98.6 |
| Lower, upper bound, % | 94.8, 98.7 | 97.2, 99.9 | 98.3, 99.9 | 97.2, 99.9 | 95.7, 99.8 |
| **Rural** | | | | | |
| Percentage complete | 86.5 | 92.5 | 90.5 | 95.7 | 86.8 |
| Lower, upper bound, % | 73.2, 95.1 | 86.0, 96.8 | 82.5, 95.9 | 87.2, 99.4 | 73.8, 95.3 |

### 6.1.2 Patient Recall of Pregnancy Testing

With S.M.A.R.T., marked improvements were seen in the percentage of women of all ages with recall of at least one pregnancy test before receiving the initial Accutane prescription (Table 10 and Table 11). Of the 9% of women who did not recall a pregnancy test before receiving their initial prescription (Table 10), 93% of these women recalled an Accutane Qualification Sticker affixed to their prescription (data not shown). However, only 64% of women (Table 11) recall having two pre-prescription pregnancy tests.

**Table 10 Women who Reported any Pregnancy Testing Before Receiving Initial Accutane Prescription – Accutane Survey (DAT-1)**

| | S.M.A.R.T. | | Pre-S.M.A.R.T. |
|---|---|---|---|
| | SEC | SI/Degge | |
| Any pregnancy test | 92% | 88% | 76% |
| Two pregnancy tests | - | 64% | - |
| No pregnancy tests | 8% | 9% | 23% |
| Unknown | <1% | 3% | 1% |

**Table 11 Patient Recall of Pre-Prescription Pregnancy Testing by Age – Accutane Survey**

Source: DAT1, Degge/S.I. only

| Age | 0-11 N=25 | 12-15 N=488 | 16-19 N=1425 | 20-29 N=2021 | 30-39 N=913 | 40-44 N=250 | 45+ N=266 | Total N=5395 |
|---|---|---|---|---|---|---|---|---|
| | (%) | (%) | (%) | (%) | (%) | (%) | (%) | (%) |
| Any pregnancy test prior to Accutane start[1] | 86% | 85% | 86% | 92% | 88% | 81% | 79% | 88% |
| Two pregnancy tests prior to Accutane Start[1] | 59% | 61% | 63% | 68% | 65% | 50% | 52% | 64% |
| Pregnancy test within 1st 5 days of menses[2] | 36% | 28% | 29% | 29% | 24% | 21% | 13% | 27% |

[1]Of the total 5395 patients, 439 patients who had not yet started Accutane or who were identified as post-hysterectomy or post-menopausal were not included in the denominator of this computation. Seven patients who are of unknown age are not included in the age-specific computations.

[2]Of the total 5395 patients, 247 patients who were identified as post-hysterectomy or post-menopausal were not included in the denominator of this computation. Also excluded are 841 who reported that they did not have a menstrual period in the 4 weeks before taking Accutane. Also excluded are 1,286 who did not report the date of their test during their menstrual period or had not received or did not report the date of Accutane prescription receipt.

### 6.1.3 Qualification Sticker versus Patient Recall of Pregnancy Testing

Some women recall use of the Accutane Qualification Sticker without recall of appropriate pre-prescription pregnancy testing (Table 12).

**Table 12 Recall of Accutane Qualification Sticker by Baseline Pregnancy Testing – Accutane Survey**

| | Qualification Sticker=Yes N=5058 | Qualification Sticker=No N=137 | Qualification Sticker Unknown N=258 |
|---|---|---|---|
| | | | |
| **Type of Pregnancy Test** | | | |
| Serum | 3682 (72.8) | 85 (62.0) | 179 (69.4) |
| Urine | 2955 (58.4) | 82 (59.9) | 147 (57.0) |
| Unknown type | 137 (2.7) | 2 (1.5) | 5 (1.9) |
| Both types | 2286 (45.2) | 55 (40.2) | 111 (43.0) |
| Any type | 4394 (86.9) | 113 (82.5) | 215 (83.3) |
| None | 664 (13.1) | 24 (17.5) | 43 (16.7) |
| | | | |
| **No. of Different (methods) Types of Tests** | | | |
| None | 664 (13.1) | 24 (17.5) | 43 (16.7) |
| 1 | 2086 (41.2) | 58 (42.3) | 103 (39.9) |
| 2 or more | 2308 (45.6) | 55 (40.2) | 112 (43.4) |
| | | | |
| **Number of Tests** | | | |
| 0 | 664 (13.1) | 24 (17.5) | 43 (16.7) |
| 1 | 1375 (27.2) | 39 (28.5) | 68 (26.4) |
| 2 | 2274 (45.0) | 60 (43.8) | 115 (44.6) |
| 3 or more | 745 (14.7) | 14 (10.2) | 32 ((12.4) |

Note: Women who indicated that they had a hysterectomy, were postmenopausal, or were not taking Accutane were excluded from this analysis.

### 6.1.4 Conclusions

Results of the Prescription Compliance Survey indicate that, for the vast majority of Accutane prescriptions, the Accutane Qualification Stickers are used and are completed correctly. However, some women in the Accutane Survey did not recall meeting the conditions for the Qualification Sticker, i.e., two pregnancy tests prior to receipt of the initial Accutane prescription, despite their recall of seeing the Qualification Sticker on their prescription.

## 6.2 Contraceptive Compliance

### 6.2.1 Results

S.M.A.R.T. requires that all female patients use two effective forms of contraception simultaneously for 1 month before, during, and 1 month following Accutane treatment. The Accutane Qualification Sticker attached to the written prescription documents that a female patient has selected and committed to use two forms of contraception simultaneously during Accutane treatment. Thus, utilization of the Qualification Sticker, assessed by the Prescription Compliance or Accutane Surveys, is a surrogate marker for a

patient's commitment to contraceptive compliance. Actual use of two effective forms of contraception was assessed using the Accutane Survey.

Few women reported being sexually active and not using any contraception. However, 18% of women reported being sexually active and not using two effective forms of contraception (Table 13). Non-compliance with the use of two forms of contraception was highest in women over the age of twenty (Table 14 and Table 15).

In addition, the presence of an Accutane Qualification Sticker on an Accutane prescription was not correlated with increased contraceptive compliance (Table 16).

## Table 13 Use of Two Forms of Contraception One of Which Was Primary* - Accutane Survey

Source: DAT1, Degge/S.I. only

| | **Total under S.M.A.R.T.[1] N=5197** |
|---|---|
| | **n(%)** |
| Hysterectomy or Post-Menopausal | 241 (5%) |
| Not sexually active [2] | 2607 (50%) |
| Sexually active | 2309 (44%) |
| % of sexually active using at least 2 forms of birth control | 1352/2309 (59%) |
| Sexually active, using at least 2 forms of birth control[3] | 1352 (26%) |
| Sexually active, not using at least 2 forms of birth control [4] | 957 (18%) |
| Percent of population who are using at least one form of birth control[5] | 3667 (71%) |
| Percent of population who are using at least two forms of birth control, one of which is a primary method[6] | 1532 (29%) |
| Unknown[7] | 40 (1%) |

* Primary methods of birth control: birth control pill, implantable hormones, injectable hormones (Depo, Lunelle), intrauterine device, hormonal vaginal contraceptive ring, tubal ligation, vasectomy.

[1] In the 4th quarter 144 (and in the total 198) women who had not yet started Accutane were excluded.

[2] The 4th quarter includes 19 (and in the total 26) women who reported that they or their partners were infertile.

[3] To qualify for this category, the patient must report using at least one primary form and at least one other (primary or secondary) form. The 4th quarter includes 125 (and in the total 179) women who reported that they or their partners were infertile. "Sexually active" includes only people who report that they are recently active. Patients who report that they have ever been active but are not currently active are classified in the "not sexually active" category.

[4] The 4th quarter includes 124 (and in the total includes 186) women who reported that they or their partners were infertile.

[5] The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using one method of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include patients the hysterectomy or postmenopausal.

[6] The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using two methods of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include the hysterectomy or postmenopausal.

[7] The 4th quarter includes 0 (and in the total includes 1) women who reported that they or their partners were infertile.

## Table 14 Use of Two Forms of Contraception One of Which Was Primary* by Age - Accutane Survey

| Age | 0-11* N=23 | 12-15 N=471 | 16-19 N=1374 | 20-29 N=1949 | 30-39 N=879 | 40-44 N=242 | 45+ N=253 | Total under S.M.A.R.T.[1] November 6, 2002 – March 31, 2003 N=5197 |
|---|---|---|---|---|---|---|---|---|
| Hysterectomy or Post-Menopausal | 1 (4%) | 0 (0%) | 2 (<1%) | 13 (1%) | 60 (7%) | 40 (17%) | 125 (49%) | 241 (5%) |
| Not Sexually active | 16 (70%) | 459 (97%) | 1123 (82%) | 777 (40%) | 166 (19%) | 33 (14%) | 29 (11%) | 2607 (50%) |
| Sexually active | 6 (26%) | 7 (1%) | 240 (17%) | 1150 (59%) | 644 (73%) | 167 (69%) | 93 (37%) | 2309 (44%) |
| % of Sexually active using at least 2 forms of birth control | 3/6 (50%) | 2/7 (29%) | 156/240 (65%) | 756/1150 (66%) | 340/644 (53%) | 71/167 (43%) | 22/93 (24%) | 1352/2309 (59%) |
| Sexually active using at least two forms of birth control | 3 (13%) | 2 (<1%) | 156 (11%) | 756 (39%) | 340 (39%) | 71 (29%) | 22 (9%) | 1352 (26%) |

*This group includes patients with computed age zero, which is likely an error in patient reporting of their birth year.

[1]A total of 198 patients who had not yet started Accutane were excluded prior to computing the overall denominator of 5197. Six patients who are of unknown age are not included in the age-specific computations.

[2]The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using one method of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include patients who have had hysterectomies or are postmenopausal.

[3]The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using two methods of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include patients who have had hysterectomies or are postmenopausal.

** Note that the percentage using a method of birth control in the age 40-44 group is 77% and most of the rest of the population (17%) has had a hysterectomy or is postmenopausal.

*** Note that the percentage using a method of birth control in the age 45 plus group is 43% and most of the rest of the population (49%) has had a hysterectomy or is post-menopausal.

## Table 14 Use of Two Forms of Contraception One of Which Was Primary* by Age - Accutane Survey (Cont.)

| Age | 0-11* N=23 | 12-15 N=471 | 16-19 N=1374 | 20-29 N=1949 | 30-39 N=879 | 40-44 N=242 | 45+ N=253 | Total under S.M.A.R.T.[1] November 6, 2002 – March 31, 2003 N=5197 |
|---|---|---|---|---|---|---|---|---|
| Sexually active, not using at least 2 forms of birth control | 3 (13%)* | 5 (1%) | 84 (6%) | 394 (20%) | 304 (35%) | 96 (40%) | 71 (28%) | 957 (18%) |
| Percent of population who are using at least one form of birth control[2] | 12 (52%) | 196 (42%) | 796 (58%) | 1615 (83%) | 746 (85%) | 187 (77%)* | 110 (43%)** | 3667 (71%) |
| Percent of population who are using at least two forms of birth control, one of which is a primary method[3] | 4 (17%) | 6 (1%) | 188 (14%) | 858 (44%) | 369 (42%) | 79 (33%) | 25 (10%) | 1532 (29%) |
| Unknown | 0 (0%) | 5 (1%) | 9 (1%) | 9 (<1%) | 9 (1%) | 2 (1%) | 6 (2%) | 40 (1%) |

[1]A total of 198 patients who had not yet started Accutane were excluded prior to computing the overall denominator of 5197. Six patients who are of unknown age are not included in the age-specific computations.

[2]The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using one method of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include patients who have had hysterectomies or are postmenopausal.

[3]The numerator includes patients who are sexually active, not sexually active or of unknown sexual activity who are using two methods of birth control. The numerator does not include the patients with hysterectomies or who are postmenopausal. Note that the population, which is the denominator for the percentage computation, does include patients who have had hysterectomies or are postmenopausal.

*Note that the percentage using a method of birth control in the age 40-44 group is 77% and most of the rest of the population (17%) has had a hysterectomy or is postmenopausal.

** Note that the percentage using a method of birth control in the age 45 plus group is 43% and most of the rest of the population (49%) has had a hysterectomy or is post-menopausal.

## Table 15 Non-Compliance with S.M.A.R.T. Contraception Requirements by Age – Accutane Survey

Source: DAT1, Degge/S.I. only ***

| Age | 0-11 N=23 | 12-15 N=471 | 16-19 N=1374 | 20-29 N=1949 | 30-39 N=879 | 40-44 N=242 | 45+ N=253 | Total[1] N=5197 |
|---|---|---|---|---|---|---|---|---|
| | (%) | (%) | (%) | (%) | (%) | (%) | (%) | (%) |
| Sexually active, not using any contraception as a percentage of overall population | 0% | 1% | 1% | 2% | 2% | 1% | 2% | 1% |
| Sexually active, not using 2 forms of contraception as a percentage of overall population | 13% | 1% | 6% | 20% | 35% | 40% | 28% | 18% |
| Not sexually active as a percentage of overall population | 70% | 97% | 82% | 40% | 19% | 14% | 11% | 50% |

[1]198 patients who had not yet started Accutane were excluded prior to computing the overall denominator of 5197. Categories do not sum to 100% because they are not mutually exclusive groups and they do not include patients with hysterectomies or those who are using contraception. Six patients who were of unknown age are not included in the age-specific computations.

**Table 16 Recall of Accutane Qualification Sticker by Contraceptive Use**

| | Accutane QS=Yes N=5058 | Accutane QS=No N=137 | Accutane QS Unknown N=258 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Not Sexually Active**** | 2700 (53.4) | 70 (51.1.) | 166 (64.3) |
| | | | |
| Not active and using birth control | 1273 (25.2) | 28 (21.4) | 73 (28.3) |
| Not active and using 2 or more forms of birth control (1 primary) | 181 (3.6) | 3 (2.2) | 7 (2.7) |
| Not active and using 1 primary form of birth control only | 865 (17.1) | 22 (16.1) | 51 (19.8) |
| Not active and using 2 or more secondary forms of birth control only | 5 (<1) | 0 | 0 |
| Not active and using 1 secondary form of birth control only | 24 (<1) | 3 (2.2) | 0 |
| Not active form of birth control not specified | 198 (3.9) | 0 | 15 (5.8) |
| Not active and not using birth control | 1427 (28.2) | 42 (31.7) | 93 (36) |
| | | | |
| **Sexually Active**** | 2358 (46.6) | 67 (48.9) | 92 (35.7) |
| | | | |
| active and using birth control | 2015 (39.9) | 52 (38.0) | 75 (29.1) |
| active and using 2 or more forms of birth control (1 primary) | 1450 (28.7) | 34 (24.8) | 56 (21.7) |
| active and using 1 primary form of birth control only | 383 (7.6) | 12 (8.8) | 15 (5.8) |
| active and using 2 or more secondary forms of birth control only | 50 (1) | 1 (<1) | 2 (<1%) |
| Not active and using 1 secondary form of birth control only | 111 (2.2) | 4 (2.9) | 1 (<1) |
| Not active form of birth control not specified | 21 (<1) | 1 (<1) | 1 (<1) |
| Not active and not using birth control | 343 (6.8) | 15 (10.9) | 17 (6.6) |
| | | | |
| **Total** | 5058 | 137 | 258 |
| | | | |
| Using birth control | 3288 (65) | 80 (58.4) | 148 (57.4) |
| Using 2 or more forms of birth control, one primary | 1631 (32.2) | 37 (27.0) | 63 (24.4) |
| Using 1 primary form of birth control | 1248 (24.7) | 34 (24.8) | 66 (25.6) |
| Using 2 or more secondary forms of brith control | 55 (1.1) | 1 (<1) | 2 (<1) |
| Using 1 secondary form of birth control | 135 (2.7) | 7 (5.1) | 1 (<1) |
| Form of birth control not specified | 219 (4.3) | 1 (<1) | 16 (6.2) |
| Not using birth control | 1770 (35) | 57 (41.6) | 110 (42.6) |

Note: Women who either had a hysterectomy, were postmenopausal and were not taking Accutane excluded.

### 6.2.2 Conclusions

Many women do not comply with the requirement for the use of two effective forms of contraception simultaneously for 1 month before, during, and 1 month following Accutane treatment. There is little relation between patient recall of a Qualification

Sticker on her prescription and her contraceptive practices. The reasons underlying these findings are unclear and cannot be ascertained from the current Accutane Survey.

## 6.3 Pregnancy Case Reports

### 6.3.1 S.M.A.R.T. versus Pre-S.M.A.R.T.

A total of 183 pregnancies were reported during S.M.A.R.T. compared to 150 pregnancies pre-S.M.A.R.T. (Table 17). The Accutane treatment initiation date was known for 94 S.M.A.R.T. pregnancies and 94 pre-S.M.A.R.T. pregnancies. The majority of S.M.A.R.T. and pre-S.M.A.R.T. pregnancies were reported directly to Roche and not to the Accutane Survey (Table 18).

**Table 17 Pregnancy Cases: S.M.A.R.T. versus Pre-S.M.A.R.T.**

| | S.M.A.R.T. | Pre-S.M.A.R.T. |
|---|---|---|
| Overall total number | 183 | 150 |
| Treatment initiation date known | 94[1] | 94[2] |
| Treatment initiation date unknown | 89[3] | 56[4] |

[1]Time period of April 1, 2002 to August 15, 2003.
[2]Time period of April 1, 2001 to August 15, 2002.
[3]Time period of April 1, 2002 to March 31, 2003.
[4]Time period of April 1, 2001 to March 31, 2002.
Data Source: Advent database

**Table 18 Source of Pregnancy Reports: S.M.A.R.T. versus Pre-S.M.A.R.T.**

| Source: | Known Therapy Start Date | | Unknown Therapy Start Date | |
|---|---|---|---|---|
| | S.M.A.R.T. | Pre-S.M.A.R.T. | S.M.A.R.T. | Pre-S.M.A.R.T. |
| Overall total number | 94 | 94 | 89 | 56 |
| Accutane Survey | 33* | 10 | 2* | 1 |
| Direct to Roche, health care professional | 46 | 60 | 48 | 36 |
| Direct to Roche, consumer or others | 15 | 24 | 39 | 19 |

*Of the 33 S.M.A.R.T. pregnancies with known Accutane initiaton dates, 11 were reported to SEC and 22 were reported to SI/Degge. Both S.M.A.R.T. pregnancies with unknown Accutane start dates were reported to SEC.

### 6.3.2 Analyses of Pregnancies

#### *6.3.2.1 Timing of Accutane Exposure Relative to Pregnancy and Pregnancy Outcome*

The majority of S.M.A.R.T. and pre-S.M.A.R.T. patients became pregnant after Accutane therapy was initiated (Table 19). A moderate decline was seen during S.M.A.R.T. for patients initiating Accutane therapy while pregnant (S.M.A.R.T., 13%; pre-S.M.A.R.T., 19%; Table 19). Similar results were seen when pregnancy cases were classified as known versus unknown Accutane start dates (Appendix page 113).

The majority of pregnancies during S.M.A.R.T. were either lost to follow-up (47.0%) or ended in therapeutic abortion (24.6%; Table 20). Similar results were seen when pregnancy cases were classified as known versus unknown Accutane start dates (Appendix page 114).

Of women with an Accutane-exposed and delivered pregnancy during S.M.A.R.T., 25% (5/20) had normal babies (Table 21). The majority of women with an Accutane-exposed and delivered pregnancy had a baby with an abnormality (birth defect, 40% [8/20]; other disorder, 25% [5/20]).

**Table 19 Timing of Exposure to Accutane Therapy Relative to Pregnancy: S.M.A.R.T. versus Pre-S.M.A.R.T.**

| | S.M.A.R.T. (N=183) | Pre-S.M.A.R.T. (N=150) |
|---|---|---|
| Pregnant when Accutane started | 24 (13%) | 28 (19%) |
| Taking Accutane when pregnancy occurred | 75 (41.0%) | 77 (51.3%) |
| Became pregnant within 30 days after stopping Accutane therapy | 58 (31.7%) | 44 (29.3%) |
| Unknown | 26 (14%) | 1 (< 1%) |

## Table 20 Timing of Exposure to Accutane versus Pregnancy Outcome: S.M.A.R.T.

| | Pregnancy Outcome | | | | | |
|---|---|---|---|---|---|---|
| | Delivery N | Lost to follow-up N | Ongoing N | Spontaneous abortion N | Therapeutic abortion N | Unknown N |
| Pregnant when Accutane started | 1 | 16 | 2 | - | 4 | - |
| Taking Accutane when pregnancy occurred | 18 | 48 | 15 | 2 | 40 | 11 |
| Unknown | 1 | 22 | - | - | 1 | 2 |
| Total* | 20 (10.9) | 86 (47.0%) | 17 (9.3%) | 2 (1.1%) | 45 (24.6%) | 13 (7.1%) |

*All percentages based on a total number of pregnancies equal to 183.

## Table 21 Pregnancy Outcome versus Offspring Status

| PREGNANCY OUTCOME | OFFSPRING STATUS | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Birth Defect | Lost to Follow-Up | Normal Baby | Other Disorder | Pregnancy Ongoing | Unknown | | |
| | N | N | N | N | N | N | N | % |
| Delivery | 8 | - | 5 | 5 | - | 2 | 20 | 10.9 |
| Lost to follow-Up | - | 86 | - | - | - | - | 86 | 47.0 |
| Pregnancy ongoing | - | - | - | - | 16 | 1 | 17 | 9.3 |
| Spontaneous abortion | - | - | - | - | - | 2 | 2 | 1.1 |
| Therapeutic abortion | - | - | - | - | - | 45 | 45 | 24.6 |
| Unknown | - | 1 | - | - | - | 12 | 13 | 7.1 |
| Total | 8 | 87 | 5 | 5 | 16 | 62 | 183 | 100.0 |

### 6.3.2.2 *Patient Age*

No differences in the age distribution of women who became pregnant were seen for S.M.A.R.T. versus pre-S.M.A.R.T. Most of the women who became pregnant were over the age of 20 years (Table 22). Approximately 17% and 16% of women who became pregnant during S.M.A.R.T. and pre-S.M.A.R.T., respectively, were under the age of 20.

**Table 22 Age of Pregnancy Cases: S.M.A.R.T. versus Pre-S.M.A.R.T.**

| Age Range | S.M.A.R.T. Year One | Pre-S.M.A.R.T. |
|---|---|---|
| 0 - 11 | - | - |
| 12 - 15 | 2 | 5 |
| 16 - 19 | 29 | 19 |
| 20 - 29 | 44 | 62 |
| 30 - 39 | 27 | 24 |
| 40 - 44 | 1 | - |
| 45+ | 1 | - |
| Unknown | 79 | 40 |
| Total | 183 | 150 |
| | | |
| Mean | 24.8 | 24.5 |
| Median | 23.0 | 24.0 |
| Range | 14 - 50 | 14 - 39 |

### 6.3.2.3 *Compliance with S.M.A.R.T. Requirements*

For those women with Accutane-exposed pregnancies during S.M.A.R.T., compliance with key S.M.A.R.T. requirements was available for 72 (Table 23). For these women, compliance with two baseline pregnancy tests and use of two forms of contraception was 40.3% and 48.6%, respectively.

**Table 23 Summary of Compliance with Selected S.M.A.R.T. Requirements – Pregnancy Cases**

Source: Advent database; S.M.A.R.T. database

| S.M.A.R.T. Parameter | N=72* | | | |
|---|---|---|---|---|
| | Yes N (%) | No N (%) | Unknown N (%) | No Information Available N (%) |
| Signed general informed consent | 58 (80.5) | 2 (2.8) | 5 (6.9) | 7 (9.7) |
| Signed female informed consent | 52 (72.2) | 3 (4.2) | 5 (6.9) | 12 (16.7) |
| Received spiral notebook | 49 (68.1) | 5 (6.9) | 3 (4.2) | 15 (20.8) |
| Received instruction for Accutane Survey | 46 (64) | 5 (6.9) | 6 (8.3) | 15 (20.8) |
| Enrolled in Accutane Survey | 26 (36.1) | 7 (9.7) | 24 (33.3) | 15 (20.8) |
| Two baseline pregnancy tests | 29 (40.3) | 16 (22.2) | 27 (37.5) | 0 |
| Monthly follow-up pregnancy tests | 41 (56.9) | 8 (11.1) | 3 (4.2) | 20 (27.8) |
| Qualification Sticker attached to prescription | 58 (80.6) | 0 | 2 (2.8) | 12 (16.7) |
| Used two forms of contraception | 35 (48.6) | 6 (8.3) | 31 (43.1) | 0 |

*Note: 22 of the 94 pregnancy cases had no S.M.A.R.T. compliance data available.

### 6.3.3 Pregnancy Rate

A pregnancy rate is reported annually by the SEC for the Accutane Survey (Table 24). This rate, which applies only to patients who participate in the Accutane Survey, was 4.0 per 1,000 Accutane treatment courses for the Survey cohort enrolled in 1989 . The rate has declined steadily to 1.8 per 1,000 Accutane treatment courses for the cohort enrolled in 2001. For the cohort enrolled in 2002, which represents the phase-in and full implementation of the S.M.A.R.T. Program, the SEC Accutane Survey rate declined to 1.2 per 1,000 Accutane treatment courses, representing a 33% drop in the risk of pregnancy among women enrolled in the Accutane Survey. It is likely that S.M.A.R.T. Program implementation contributed to this decrease in the pregnancy rate.

A pregnancy rate for the first enrollment cohort for the S.I./Degge Accutane Survey (November 2002 – December, 2003) will be available in the third quarter of 2004.

A key limitation to the pregnancy rates reported by the Accutane Survey is that they apply only to women who have participated in the Survey. Because not all female patients enroll in the Survey, the rate may not be representative of the entire female Accutane population.

## Table 24 Accutane Survey Pregnancy Rates over Time

| | Number of Pregnancies per 1000, 140-Day Accutane Treatment Courses | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Enrollment Year** | **1989** | **1990** | **1991** | **1992** | **1993** | **1994** | **1995** | **1996** | **1997** | **1998** | **1999** | **2000** | **2001** | **2002** |
| | 4.0 | 3.6 | 3.0 | 3.0 | 2.7 | 2.4 | 2.8 | 2.7 | 2.5 | 2.1 | 2.2 | 1.6 | 1.8 | 1.2 |

### 6.3.4 Conclusions

Moderate decreases were seen with S.M.A.R.T. in the number of women who initiated Accutane therapy while pregnant; however, the absolute number of pregnancies has not changed with S.M.A.R.T. Available data pertaining to compliance with S.M.A.R.T. Program requirements indicate that pregnancy is associated with incomplete compliance with one or more parameters.

## 7. OVERALL ASSESSMENT

Overall the S.M.A.R.T. program evaluation data indicate that the mechanics of the Qualification Sticker have been successfully implemented, with metrics for the Prescription Compliance Survey, and patient recall of seeing the Qualification Sticker in the Accutane Survey exceeding 90%. The proportion of patients with recall of at least one pre-prescription pregnancy test in the Accutane Survey has improved from 76% to 91%. The proportion of women who were already pregnant when they received their first Accutane prescription fell to 13% from 19% the year prior. Accutane Survey enrollment from the prescriber's office more than doubled, suggesting increased prescriber involvement with encouraging patients to enroll in the Accutane Survey.

Other indicators suggest that further pregnancy risk management activities are needed. The percentage of women who recall two baseline pregnancy tests are low, as are the percentages of women who report that they consistently use two forms of contraception according to program requirements. The link between patient recall of a Qualification Sticker and patient recall of pregnancy testing and contraceptive compliance in the Accutane Survey is not sufficiently robust. Despite improved enrollment in the Accutane Survey, the 60% enrollment metric was not met, and the representativeness of participants in a voluntary survey to non-participants continues to be questioned.

Finally, the overall number of reported pregnancies has not decreased, despite the decrease in the percentage of women who initiate Accutane therapy while pregnant. This could be due to either: 1) increased pregnancy reporting because S.M.A.R.T. has increased public awareness or 2) lack of contraceptive compliance.

The totality of the data suggest that further modifications to the isotretinoin pregnancy risk management program are appropriate.

## 8. PROPOSED PROGRAM ENHANCEMENTS FOR ISOTRETINOIN RISK MANAGEMENT

### 8.1 Background and Rationale

On December 10, 2003, the Agency held a meeting with the companies currently manufacturing and marketing isotretinoin in the US. At this meeting, the Agency expressed concern, that based on a preliminary review of data from all companies, the total number of pregnancies remain within the same range as pre-S.M.A.R.T.

In particular, the Agency noted the following data from the pregnancy prevention programs:

- Data from the Prescription Compliance Survey and corroborated by patients in the respective isotretinoin Surveys indicate that well over 90% of dispensed prescriptions contain the Qualification Sticker.
- Among all women who reported receiving a prescription with a Qualification Sticker, 90% reported receiving a baseline pregnancy test.
- 9% of women who recalled a sticker on their prescription did not recall receiving a pregnancy test, i.e., the sticker is not always providing an absolute link between negative pregnancy status and dispensing of a prescription.

A proposal for a modified istotretinoin risk management program is outlined in Table 25 and Figure 2. A draft image of a revised isotretinoin Qualification Sticker is also included in Figure 2.

The program includes the key components of a back-up program as requested in the Agency's approval letter for S.M.A.R.T. (Appendix page 97 ) on October 30, 2001 and corresponding approval letters for the ANDA products.

The proposal includes mandatory registration with a third party system of all prescribers of isotretinoin, all isotretinoin patients, and pharmacy registration for dispensing isotretinoin. It calls for separate risk management activities for females of childbearing potential, including pregnancy testing by an accredited laboratory, and regular interaction by all patients, prescribers, and pharmacists with the risk management system. The pregnancy prevention elements of the proposal are described in detail in Table 25 and Figure 2.

**Table 25 Key Elements of the Proposed Risk Management Program**

1. All patients (males and females) diagnosed by a registered prescriber to be a candidate for isotretinoin therapy must enroll into the registry.
2. "Childbearing potential" and "Not of childbearing potential" (including males, post-menopausal females, etc.,) to be decided by the registered prescriber as per guidelines in the PI.
3. Current education and Informed Consent process is followed. This includes consent for patient to be placed into a third party database.
4. The Registry will be a single system for all manufacturers. The registry will assign a patient identification number (PIN) which can uniquely identify the patient in all future transactions. The system will contain an educational and risk management evaluation component that all patients will be required to complete before receiving isotretinoin.
5. Registration information to include specific information to uniquely identify the patient. Transmission of registration information from registered prescriber's office to the registry and back.
6. Education, consultation, and registration of all patients occurs. During the consultation, the registered prescriber will educate the patient regarding the need for isotretinoin, the risks associated with treatment, and all procedures as outlined in the isotretinoin risk management program. All patients will be qualified, registered, and required to interact with a system-based educational and risk management evaluation component as per their requirements.
7. For eligible patients, a prescription for 30 days of isotretinoin and a Qualification Sticker is affixed to the prescription.
8. Patient takes prescription to a registered pharmacy. Pharmacies register by reading a *Guide to Best Practices for Pharmacists* and completing a *Pharmacy Letter of Understanding*.
9. Registered pharmacy checks with registry (submitting PIN and other to be identified information) to determine if prescription can be dispensed. Prescription can only be dispensed if patient meets all qualification criteria per their PI requirements including appropriate responses to the patient educational and risk management evaluation component of the system.
10. Registry issues a YES or NO and invalidates the records in the database so that the prescription cannot be filled by another pharmacy.
11. Pharmacy to dispense isotretinoin if the registry says YES and enters authorization number on prescription. If NO, patient is advised to contact prescriber.
12. Prior to dispensing, pharmacist enters product NDC code, LOT #, etc., into system.
13. For all isotretinoin prescriptions after the initial one, the patient will require re-qualification including re-education by the prescriber and the patient will need to again interact with the patient educational and risk management evaluation component of the system. The prescriber will enter the re-qualification information into the system.

## Table 25 Key Elements of the Proposed Risk Management Program (Cont.)

**For females of childbearing potential only:**

14. First pregnancy test is done as a screening test in the prescriber's office and under supervision of a staff member. If this test is positive, the patient is not eligible for the isotretinoin.
15. The patient is required to get a pregnancy test done by an accredited laboratory. This second test is a confirmatory test and is done on a date derived from the guidelines in the PI for the initial prescription.
16. For all isotretinoin prescriptions after the initial one, the patient will require re-qualification including re-education by the prescriber, a negative pregnancy test conducted by an accredited laboratory, and interaction with the patient educational and risk management evaluation component of the system. The prescriber will enter the re-qualification information into the system.
17. Pregnancy test results conducted by an accredited laboratory are electronically transmitted to the registry and the prescriber.
18. Centralized reporting and follow-up for all pregnancies.

## Figure 2 Process Map

## 8.2 Links between Previous Accutane Pregnancy Risk Management Programs and the Current Proposal

The current proposal preserves much of what has already been established in the previous risk management programs for isotretinoin pregnancy prevention (see Table 3). No significant changes are planned for the following:

- Initial prescriber registration process and requirements.
- Patient and prescriber printed educational materials.
- Patient informed consent processes/requirements.
- Isotretinoin limited to 30-day supply with no refills.
- Use of written prescriptions only with a properly-completed Qualification Sticker attached (no telephone or computerized prescriptions are permitted).
- Prescription fill time limit.
- Isotretinoin packaging.
- Labeled requirements for pregnancy testing and contraceptive use.

### 8.2.1 Enhancements to Current Isotretinoin Pregnancy Risk Management

The proposal calls for enhancing the links between prescriber, patient, and pharmacy, and enhancing the link between a negative confirmatory pregnancy test and product dispensing, all of which were established under the S.M.A.R.T. Program. Enhancements are achieved by the following:

- Registration and qualification of all patients in a single information system.
- System-based re-qualification of all patients including patient interaction with a system-based patient educational and risk management evaluation component of the system for each isotretinoin prescription.
- Transmission of the results of a pregnancy test conducted by an accredited laboratory to the system and to the prescriber for females of childbearing potential.
- Registration of all pharmacies for dispensing isotretinoin. Registration includes review of the *Guide to Best Practices for Pharmacists* and signing and returning the *Pharmacist Letter of Understanding*.
- Registered, dispensing pharmacy confirmation of patient qualifications in the system.
- Identification of product and amount dispensed in the system.

The links between the proposed new program, the PPP, and S.M.A.R.T. and equivalent programs are summarized in Table 26.

## Table 26 Evolution of Isotretinoin Risk Management Program

| Item | PPP | S.M.A.R.T and Equivalent Programs* | Proposed Program |
|---|---|---|---|
| | | | |
| **Educational Materials** | | | |
| Prescriber materials | Accutane Prescribers' and Healthcare Professionals' Guide | 1. S.M.A.R.T. *Guide to Best Practices*<br>2. Letter of understanding and self-addressed postage-paid envelope<br>4. *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane® (isotretinoin)*<br>3. Yellow self-adhesive Qualification Sticker | Unchanged except for format of self-adhesive Qualification Sticker to accommodate patient authorization codes |
| Pharmacist materials | | *Dear Pharmacist Letter* that described S.M.A.R.T. | *Guide to Best Practices for Pharmacists* and *Pharmacist Letter of Understanding* |
| Female patient materials | 1. Patient folder containing educational and qualification materials[1]<br>2. Medication guide<br>3. *Be Prepared, Be Protected* Video<br>4. Free urine pregnancy tests | 1. Comprehensive booklet, *Be Smart, Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women*, with 3 discrete sections[2]:<br>2. Medication Guide<br>3. *Be Prepared, Be Protected* Video<br>4. *Be Aware, The Risks of Pregnancy While on Accutane*, a birth defects video | Female materials unchanged from S.M.A.R.T. |
| Male patient materials | 1. Patient brochure: Important Information Concerning your Treatment with Accutane<br>2. Informed consent/patient agreement | 1. Comprehensive booklet, *Be Smart, Be Safe, Be Sure™: Accutane Risk Management Program for Men* with 3 discrete sections[3]<br>2. Informed consent/patient agreement<br>3. Medication Guide | Male materials unchanged from S.M.A.R.T. |

*S.P.I.R.I.T., I.M.P.A.R.T., and A.L.E.R.T.

## Table 26 Evolution of Isotretinoin Risk Management Program (Cont.)

| Item | PPP | S.M.A.R.T and Equivalent Programs* | Proposed Program |
|---|---|---|---|
| **Process Requirements** | | | |
| Prescriber | Review patient booklet and counsel patient; supply patient booklet and have patient sign all forms. Encourage patient to use reinforcement materials; help female patient of childbearing potential select 2 forms of effective contraception or refer patient to a contraception counselor, reimbursed by Roche. | As for PPP plus female patient qualification (negative pregnancy test, encourage to enroll in Accutane Survey, informed consents, females of childbearing potential select and commit to use 2 separate forms of effective contraception); attachment and completion of Qualification Sticker according to *Prescriber Letter of Understanding* | As for S.M.A.R.T., plus registration and qualification of all patients in system for each prescription; documentation of patient registration/qualification on Qualification Sticker. |
| Male patients and females not of childbearing potential | Review patient education materials and informed consent | As for PPP | As for S.M.A.R.T., but pt must also interact with education and risk management evaluation component of the system for each prescription. |
| Female patients of childbearing potential | Patient education materials and informed consent, informed consent for female patients, baseline and monthly negative pregnancy test; select and use 2 forms of contraception; wait until next period after negative baseline test to start Accutane; | As for PPP with addition of second, properly timed, confirmatory negative pregnancy test for initial prescription | As for S.M.A.R.T., but confirmatory negative pregnancy test must be conducted by an accredited laboratory with results transmitted to the system. Patient must also interact with education and risk management evaluation component of the system for each prescription. |
| **Prescribing requirements** | Routine practice | 30 day supply; no refills; no telephone or computer-generated Rx's; completed yellow Qualification Sticker attached to each Rx with patient qualification date. | As for S.M.A.R.T. plus system-generated patient ID number required on Qualification Sticker for all patients |

*S.P.I.R.I.T., I.M.P.A.R.T., and A.L.E.R.T.

## Table 26 Evolution of Isotretinoin Risk Management Program (Cont.)

| Item | PPP | S.M.A.R.T and Equivalent Programs* | Proposed Program |
|---|---|---|---|
| **Dispensing requirements** | Special packaging and medication guide for female patients | As for PPP plus 30 day supply only; no refills; no telephone or computer-generated Rx's; completed yellow Qualification Sticker attached to each Rx with patient qualification date, qualification date on sticker must be within 7 days of fill date | As for S.M.A.R.T. plus dispensing pharmacies must be registered. Registered pharmacy checks system for Rx authorization for all patients and documents it; dispensing pharmacy and product and amount dispensed to all patients identified in system |

*S.P.I.R.I.T., I.M.P.A.R.T., and A.L.E.R.T.

[1]Female materials in patient folder included 10 printed items: patient brochure Important Information Concerning Your Treatment with Accutane, Some Important Things to Remember—5 Steps to Contraception Counseling Referral, Accutane Survey Enrollment Form, Informed Consent/Patient Agreement for all patients, Patient Information/Consent for female patients, Qualification Checklist for for Placing Women of Childbearing Potential on Accutane, Patient Self-Evaluation, Birth Control: The Facts You Need, AlertLine, Medication Guide.

[2]Contents of *Be Smart*, *Be Safe, Be Sure™: Accutane Pregnancy Prevention and Risk Management Program for Women* are:

Education: Important Information Concerning Your Treatment with Accutane (isotretinoin); Contraception Counseling Referral Form

Consent: Accutane Survey Enrollment Form, Informed Consent/Patient Agreement for all patients, patient information/Consent for female patients, Patient Qualification Form for Pregnancy Prevention and Contraceptive Compliance

Education Reinforcement: Preventing Pregnancy—A Guide to Contraception, Confidential Contraception Counseling Line, Accutane InfoLine, Scenes from Be Prepared, Be Protected video, Contraception Knowledge Test.

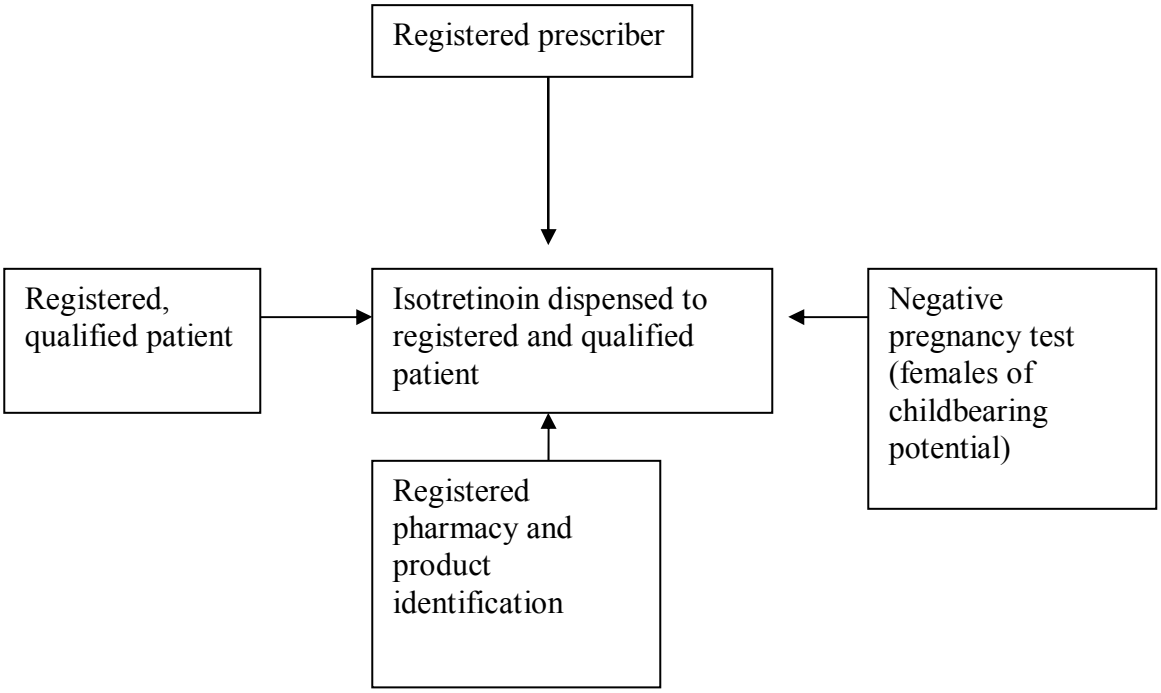
[3]Contents of *Be Smart, Be Safe, Be Sure™: Accutane Risk Management Program for Men* are:

- Education: Reproduction information, Important Information Concerning Your Treatment with Accutane (isotretinion)
- Consent: Informed Consent/Patient Agreement for all patients
- Education Reinforcement: Accutane InfoLine

The proposal for an enhanced isotretinoin pregnancy risk management program includes a single information system that provides a verifiable link between the registered prescriber, all registered patients, the results of a pregnancy test conducted by an accredited laboratory (for females of childbearing potential only), and the registered pharmacy that dispenses isotretinoin to the patient (Figure 3). The system would also capture the identity and amount of product dispensed.

Analyses of data from the system would be provided to each manufacturer for safety reporting and program evaluation purposes and to the FDA.

**Figure 3 Proposal for Enhanced Isotretinoin Risk Management Program**




### 8.2.2 Key Components of the Proposal

Key components of the program include the following:

- Mandatory prescriber registration.
- Mandatory registration of all patients, males and females.
- Mandatory registration of pharmacies.
- Prescriber attestation of patient education/qualification in the system for each isotretinoin prescription.
- Mandatory patient interaction with the educational and risk management evaluation component of the system.

- Mandatory reporting to the system of the results of a pregnancy test (for female patients of childbearing potential) conducted by an accredited laboratory within an appropriate time frame.
- Mandatory use of a Qualification Sticker on each isotretinoin prescription.
- Dispensing of isotretinoin to patient only if system authorizes it.
- Mandatory identification of product and amount dispensed.
- Centralized mechanism for reporting and follow-up of pregnancies.

Each proposed component is further described below.

#### *8.2.2.1 Mandatory Registration of Practitioners Prescribing Isotretinoin*

Each prescriber who wishes to prescribe isotretinoin would need to register in the Isotretinoin Pregnancy Risk Management System, in much the same manner as under the current pregnancy prevention programs. Registration would be accomplished as follows:

- Prescriber receives program registration materials.
- Prescriber reads a *Guide to Best Practices* for prescribing isotretinoin.
- Prescriber completes and returns a *Letter of Understanding*.
- Registration allows the prescriber to receive a supply of self-adhesive isotretinoin Qualification Stickers that must be affixed to each isotretinoin prescription. For female patients, the Qualification Sticker would include space for the prescriber to write a unique patient identification number issued by the system once the prescriber registers and qualifies the patient in the system.

#### *8.2.2.2 Mandatory Registration of All Patients, Males and Females*

All patients would be registered, qualified, and requalified monthly in the system by the prescriber. Patient education, informed consent, and qualification requirements differ based on whether or not a patient is a female of childbearing potential

**Patients not of childbearing potential.** If the patient is judged by the prescriber to be not of childbearing potential (e.g., male, post-menopausal, hysterectomy), the patient is registered as such in the system. Patients not of childbearing potential would receive isotretinoin education, the comprehensive booklet describing the isotretinoin risk management program, and signing of an informed consent/patient agreement form. Once this is completed, the patient would be registered and qualified to receive his/her prescription without going through the pregnancy prevention processes. For each prescription, the patient will be required to interact with the patient educational and risk management evaluation component of the system and would be required to have each prescription authorized in the system monthly.

**Females of childbearing potential.** Female patients of childbearing potential are to receive an initial screening pregnancy test (urine is acceptable) in the prescriber's office. If this initial screen is positive, the isotretinoin process is stopped until the patient is confirmed as not pregnant.

If the screening pregnancy test is negative, the prescriber either proceeds with appropriate patient education and counseling regarding isotretinoin therapy, and in particular,

contraceptive use and pregnancy prevention prior to, during, and for 30 days following isotretinoin therapy or refers the patient to a contraceptive counselor. This includes patient viewing of the isotretinoin videos, review of the comprehensive written materials for isotretinoin pregnancy prevention and risk management for women, and patient selection of and commitment to use two separate forms of effective contraception for 1 month prior to, during, and 30 days after stopping isotretinoin therapy. The patient signs both the general informed consent for isotretinoin therapy and the female patient informed consent. Prior to receiving each prescription, the patient must interact with the educational and risk management evaluation component of the system.

#### *8.2.2.3 Prescriber Attestation of Patient Education/Qualification in the System for each Isotretinoin Prescription*

Once the patient has been educated and counseled as specified in the PI, and signed the patient consent form(s), the prescriber registers the patient in the system and documents his/her qualifications including that he/she has received the appropriate education, the two forms of contraception she has committed to use (females of childbearing potential only), and that he/she has signed the appropriate patient consent form(s)s. The system produces a unique identification number for the patient, which the prescriber writes on the Qualification Sticker attached to the written prescription

#### *8.2.2.4 Mandatory Reporting to the System of the Results of a Confirmation Pregnancy Test Conducted by an Accredited Laboratory within the Appropriate Time Frame (For Females of Childbearing Potential Only)*

During the first 5 days of the menstrual period immediately preceding the planned start of isotretinon therapy (i.e., at least 1 month after appropriate contraceptive use and at least 11-14 days after the last act of unprotected sexual intercourse for patients with amenorrhea), the patient is required to have a laboratory-conducted, confirmation pregnancy test, the results of which are electronically reported to the prescriber and to the system. The specific mechanism for reporting the results to the system is to be determined. If the test is positive, the isotretinoin prescription is not authorized.

#### *8.2.2.5 Mandatory Registration of Pharmacies*

In order to dispense isotretinoin, the pharmacy needs to register in the Isotretinoin Pregnancy Risk Management System. Registration would be accomplished as follows:

- Pharmacy receives program registration materials.
- Pharmacist reads the *Guide to Best Practices for Pharmacists.*
- Pharmacy completes and returns a *Letter of Understanding for Pharmacists.*
- Pharmacy receives authorization to access the system and dispense isotretinoin.

#### *8.2.2.6 Mandatory Qualification Sticker on Each Isotretinoin Prescription*

All isotretinoin prescriptions (male and female) will have a self-adhesive Qualification Sticker attached (Figure 2). The Qualification Sticker will indicate whether a patient is male or female. The Qualification Sticker will also contain system access instructions for

all patients including a unique identification number for use by the registered, dispensing pharmacy to identify the patient in the system.

#### *8.2.2.7 Dispensing of Isotretinoin only if System Authorizes It*

Upon presentation of an isotretinoin prescription for a patient with the Qualification Sticker attached, the registered dispensing pharmacy will access the system (method to be determined) and verify that the prescription is authorized. For all patients, if the system lacks prescriber authorization or appropriate patient responses to the patient educational and risk management evaluation components, the system will indicate to the pharmacist that the prescription is not valid and that the patient should be instructed to return to the prescriber. Additionally, for females of childbearing potential, negative pregnancy test results must be in the system. If more than 7 days has passed since the specimen for pregnancy testing was obtained, the system will indicate to the pharmacist that the prescription is not valid and that the patient should be instructed to return to the prescriber. If all respective criteria are met for the patient, the system will authorize the prescription and the pharmacist is free to dispense isotretinoin after entering pharmacy and drug identification information. Pharmacist writes the authorization code on the Qualification Sticker.

#### *8.2.2.8 Mandatory Identification of Product and Amount Dispensed*

The pharmacist will enter identifying information about the product and the amount being dispensed (e.g., NDC code (s), lot#) into the system prior to dispensing.

For all patients, the process identified previously must be repeated every 30 days for the duration of isotretinoin therapy.

#### *8.2.2.9 Centralized Pregnancy Reporting and Follow-Up*

A centralized system for reporting, confirming, and follow-up of all pregnancies (e.g., a pregnancy registry) should be established and would represent an important modification to current decentralized pregnancy reporting procedures. A systematic approach to pregnancy reporting and follow-up would enhance failure-analysis efforts and facilitate the calculation of an isotretinoin-exposed pregnancy rate. Further work is necessary to establish the details of establishing a centralized system.

Additionally, with the interactive education and pregnancy registry, Roche believes that neither the Prescription Compliance Survey nor the Accutane Surveys would be necessary.

### 8.3 Conclusions

The proposed risk management program enhancements establish a verifiable link between the prescriber, the patient, a pregnancy test conducted by an accredited laboratory, and the dispensing of isotretinoin. Isotretinoin will not be allowed to be dispensed to any patient unless the system verifies the following:

- Prescriber registration.
- Patient registration.

- Prescriber qualification of the patient in the system.
- Appropriate patient interaction with the education and risk management evaluation component of the system.
- Pharmacy registration.

Additionally, for females of childbearing potential, a negative pregnancy test conducted by an accredited laboratory is required. This approach may reduce the numbers of women who are pregnant when they receive an initial prescription for isotretinoin by reducing errors that may be occurring with implementing the initial pregnancy testing and contraceptive use requirements as they currently exist in the PI. The fundamental pregnancy testing and contraceptive use requirements for the initial isotretinoin prescription remain unchanged.

Although there is no way to absolutely ensure correct contraceptive use during treatment, the requirements for re-qualification of the patient in the system for subsequent isotretinoin prescriptions provides a process that regularly reinforces with both the patient and the prescriber the requirements for appropriate isotretinoin risk management as described in the PI. This may reduce the risk of errors that may currently be occurring with monthly pregnancy testing and contraceptive use. This may reduce the number of women who become pregnant during isotretinoin therapy. The fundamental pregnancy testing and contraceptive use requirements for ongoing isotretinoin therapy do not change. The requirement for the results of a negative pregnancy test in the system conducted by an accredited laboratory should also facilitate early and confirmed detection of pregnancies that may occur during treatment.

The system will provide improved capabilities for auditing compliance with the risk management program and for program evaluation. Pharmacists will not be able to access the system without being registered to dispense isotretinoin. Pharmacists will be required to identify the product and amount being dispensed in the system and to record a prescription authorization number on the Qualification Sticker. This will facilitate audits of pharmacy compliance with the system, and the ability to link specific prescribers, patients, pharmacies, and pregnancy test results to specific prescriptions.

The system will facilitate the conduct of pregnancy risk management evaluation activities in a representative fashion, including the following:

- Calculation of a pregnancy rate.
- Improved failure analysis for pregnancies that occur.
- Identification of risk factors for the occurrence of pregnancy.
- Assessment of patient knowledge of isotretinoin teratogenicity.
- Assessment of compliance with and effectiveness of program requirements.
- Identification of areas for future program enhancements.

Evaluations of the effectiveness of and compliance with pregnancy risk management programs for isotretinoin have historically been of a voluntary nature and have included the Accutane and respective Isotretinoin Surveys, the Prescription Compliance Survey, and voluntary reporting of isotretinoin-exposed pregnancies to the companies. The proposed program allows for the development of alternatives to both the Isotretinoin and

Prescription Compliance Surveys that will accomplish their objectives and more in a reliable and efficient manner. Centralized reporting and systematic follow-up of isotretinoin-exposed pregnancies will also enhance program evaluation. It should be noted that mandatory female patient enrollment and a laboratory-based reporting system for pregnancy testing results may result in an initial increase in the numbers of reported pregnancies.

## 9. REFERENCES

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**ACCUTANE®**

**(isotretinoin)**

**CAPSULES**

**$R_X$ only**

**CAUSES BIRTH DEFECTS**

**DO NOT GET PREGNANT**

## CONTRAINDICATIONS AND WARNINGS

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

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

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

**Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported.**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**INFORMATION FOR PHARMACISTS:**

**ACCUTANE MUST ONLY BE DISPENSED:**

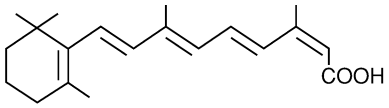
- **IN NO MORE THAN A 30-DAY SUPPLY**
- **ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **WITHIN 7 DAYS OF THE QUALIFICATION DATE**
- **REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **NO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

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

## DESCRIPTION

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

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




## CLINICAL PHARMACOLOGY

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

## Nodular Acne

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

## Pharmacokinetics

### Absorption

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

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

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

*Eating a standardized high-fat meal

### Distribution

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

### Metabolism

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

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

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

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

### Elimination

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

## Special Patient Populations

### Pediatric Patients

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

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

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

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

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

## INDICATIONS AND USAGE

### Severe Recalcitrant Nodular Acne

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

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

## CONTRAINDICATIONS

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

### Allergic Reactions

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

## WARNINGS

### Psychiatric Disorders

**Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane® (isotretinoin).***

### Pseudotumor Cerebri

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

### Pancreatitis

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

### Lipids

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

have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane.[5]

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

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

### Hearing Impairment

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

### Hepatotoxicity

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

### Inflammatory Bowel Disease

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

## Skeletal

### Bone Mineral Density

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

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

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

### Hyperostosis

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

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

require a longer time frame to appear. The clinical course and significance remain unknown.

### Premature Epiphyseal Closure

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

## Vision Impairment

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

### Corneal Opacities

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

### Decreased Night Vision

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

## PRECAUTIONS

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

The following further describes each component:

1) The S.M.A.R.T. *Guide to Best Practices* includes: Accutane teratogenic potential, information on pregnancy testing, specific information about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy, the methods to evaluate pregnancy risk, and the method to complete a qualified Accutane prescription.

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

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

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

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

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

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

video "Be Prepared, Be Protected" and the video "Be Aware: The Risk of Pregnancy While on Accutane".

### General

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

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

### Information for Patients and Prescribers

- Patients should be instructed to read the Medication Guide supplied as required by law when Accutane is dispensed. The complete text of the Medication Guide is reprinted at the end of this document. For additional information, patients should also read the *Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin)*. All patients should sign the Informed Consent/Patient Agreement.
- Females of childbearing potential should be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Accutane, while taking Accutane, and for 1 month after Accutane has been stopped. They should also sign a consent form prior to beginning Accutane therapy. They should be given an opportunity to enroll in the Accutane Survey and to review the patient videotapes provided by the manufacturer to the prescriber. The videos include information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a woman who is pregnant takes Accutane at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).

- Accutane is found in the semen of male patients taking Accutane, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.
- Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether or not Accutane therapy is appropriate in this setting (see WARNINGS: Psychiatric Disorders).
- Patients should be informed that they must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events.
- Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane.
- Patients should be reminded to take Accutane with a meal (see DOSAGE AND ADMINISTRATION). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.
- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.
- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS: Skin and Appendages).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted (see ADVERSE REACTIONS: Musculoskeletal). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see Laboratory Tests: CPK).
- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane. Consideration should be given to discontinuation of Accutane if any significant abnormality is found.

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

### Hypersensitivity

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

### Drug Interactions

- *Vitamin A:* Because of the relationship of Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- *Tetracyclines:* Concomitant treatment with Accutane and tetracyclines should be avoided because Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used combined oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see boxed CONTRAINDICATIONS AND WARNINGS).
- *Phenytoin:* Accutane has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane. Therefore, caution should be exercised when using these drugs together.
- *Systemic Corticosteroids*: Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane. Therefore, caution should be exercised when using these drugs together.

Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. **Accutane use is associated with**

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

## Laboratory Tests

### Pregnancy Test

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

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

- *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see WARNINGS: Lipids).
- *Liver Function Tests:* Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS: Hepatotoxicity).
- *Glucose:* Some patients receiving Accutane have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane therapy, although no causal relationship has been established.
- *CPK:* Some patients undergoing vigorous physical activity while on Accutane therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

### Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Accutane (isotretinoin) therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

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

### Nursing Mothers

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

### Pediatric Use

The use of Accutane in pediatric patients less than 12 years of age has not been studied. The use of Accutane for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those

patients where a known metabolic or structural bone disease exists (see PRECAUTIONS: General). Use of Accutane in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (≥18 years). Results from this study demonstrated that Accutane, at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

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

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

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

### Geriatric Use

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

## ADVERSE REACTIONS

### Clinical Trials and Postmarketing Surveillance

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

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

### Dose Relationship

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

#### Body as a Whole

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

#### Cardiovascular

palpitation, tachycardia, vascular thrombotic disease, stroke

#### Endocrine/Metabolic

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

#### Gastrointestinal

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

#### Hematologic

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

#### Musculoskeletal

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

#### Neurological

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

### Psychiatric

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

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

### Reproductive System

abnormal menses

### Respiratory

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

### Skin and Appendages

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

### Special Senses

#### *Hearing*

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

#### *Vision*

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

### Urinary System

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

## Laboratory

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

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

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

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

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

## OVERDOSAGE

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

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

## DOSAGE AND ADMINISTRATION

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

The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

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

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

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

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

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

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

**Information for Pharmacists**

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

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

## HOW SUPPLIED

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

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

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

### Storage

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

## 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/CONSENT (for female patients concerning birth defects)

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

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

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

_____

(Patient's Name)

1. I understand that there is a very high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Accutane in any amount even for short periods of time. This is why I must not be pregnant while taking Accutane.

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

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

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

    Initial: _____

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

    Initial: _____

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

    Initial: _____

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

    Initial: _____

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

    Initial: _____

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

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

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

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

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

    Initial: _____

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

Initial: _____

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

Patient Signature:_____ Date:_____

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

Please print: Patient Name and Address_____
_____ Telephone _____

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

Prescriber Signature: _____ Date:_____

## INFORMED CONSENT/PATIENT AGREEMENT (for all patients):

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

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

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

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

    Initials: _____

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

    Initials: _____

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

    Initials: _____

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

Patient Signature: _____ Date: _____

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

Patient Name (print) _____

Patient Address _____ Telephone (___.___.___)

_____

I have:

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

Prescriber Signature: _____ Date:_____

## MEDICATION GUIDE

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

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

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

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

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

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

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

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

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

## What are the important warnings for females taking Accutane?

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

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

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

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

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

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

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

***All patients should read the rest of this Medication Guide.***

## What are the signs of mental problems?

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

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

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

### What is Accutane?

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

### Who should not take Accutane?

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

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

### How should I take Accutane?

- You will get no more than a 30-day supply of Accutane at a time, to be sure you check in with your prescriber each month to discuss side effects.
- Your prescription should have a special yellow self-adhesive sticker attached to it. The sticker is YELLOW. If your prescription does not have this yellow self-adhesive sticker, call your prescriber. The pharmacy should not fill your prescription unless it has the yellow self-adhesive sticker.

- The amount of Accutane you take has been specially chosen for you and may change during treatment.
- You will take Accutane 2 times a day with a meal, unless your prescriber tells you otherwise. Swallow your Accutane capsules with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.
- If you miss a dose, just skip that dose. Do **not** take 2 doses the next time.
- You should return to your prescriber as directed to make sure you don't have signs of serious side effects. Because some of Accutane's serious side effects show up in blood tests, some of these visits may involve blood tests (monthly visits for female patients should always include a urine or serum pregnancy test).

### What should I avoid while taking Accutane?

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

- **Do not take Accutane with antibiotics unless you talk to your prescriber.** For some antibiotics, you may have to stop taking Accutane until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain.

### What are the possible side effects of Accutane?

**Accutane has possible serious side effects**

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

needed treatment. These problems generally go away when Accutane treatment is finished.

- **Allergic reactions.** In some people, Accutane can cause serious allergic reactions. Stop taking Accutane and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Accutane may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

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

## Accutane has less serious possible side effects

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

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

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

## Active Ingredient: Isotretinoin.

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

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

Roche Pharmaceuticals

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

27898602

Revised: August 2003

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-662/S-044

Hoffmann-La Roche Inc.
Attention: Joanna Waugh, BSc., Hons,
Group Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, N. J. 07110

30 OCT 2001

Dear Ms. Waugh:

Please refer to your supplemental new drug application dated September 17, 2001, received September 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) capsules, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated October 4, 8, 9 (2), and 25 (facsimile), 2001.

This supplemental new drug application provides for revisions to labeling to reflect the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Program, an enhanced risk management program to help prevent fetal exposure to Accutane. In addition, this application specifies several evaluation metrics including those related to 1) female participation in the Accutane Survey conducted by the Slone Epidemiology Unit of Boston University, and 2) prescriber and pharmacist compliance with the use of Accutane qualifying stickers.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert; patient *Informed Consent* forms; *Medication Guide*; booklet for prescribers entitled *System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Guide to Best Practices*; Prescriber Checklist; *S.M.A.R.T. Letter of Understanding for Prescribers; Accutane Qualification Sticker;* Pharmacist *Accutane Dispensing Guide*; Carton Dispensing Instructions; FDA Letter to Pharmacy Boards; *Dear Accutane Prescriber Letter*; *Dear Pharmacist Letter*; *Be Smart, Be Safe, Be Sure for Women; Be Smart, Be Safe, Be Sure for Men*; immediate container and carton labels).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved

supplement NDA 18-662/S-044." Approval of this submission by FDA is not required before the labeling is used.

The following are conditions for approval of this labeling supplement:

1. All of the components and tools associated with S.M.A.R.T. and/or described in the appended documents are conditions for approval. The only exceptions are the Continuing Medical Education seminar, the free urine pregnancy test kits, and the progress note pads for prescribers. We recognize the utility of these components, but consider them optional because, by definition, the prescriber commits to obtaining adequate training and patient pregnancy testing in order to receive the Qualification Stickers.

2. You should either place the *Medication Guide* into the unit packaging with implementation of S.M.A.R.T. or submit within 30 days an amended version (based on consumer comprehension testing). If the Medication Guide is not placed into the unit packaging now, you should submit, within one week, documentation that all retail outlets for Accutane, including legal on-line pharmacies, have been sent an adequate re-supply of Medication Guides.

3. A plan should be submitted within one week for ensuring, to the greatest practical extent, that all packages and documents in the marketplace are the new approved materials as soon as possible.

4. The adequacy of S.M.A.R.T will be a review issue for re-evaluation on a continuing basis. The Plan for a back-up program should include:

   - Mandatory registration of all patients both male and female receiving Accutane
   - Mandatory registration and certification of practitioners prescribing Accutane
   - Mandatory reporting of all fetal exposures to Accutane
   - Mandatory restricted distribution through registered pharmacies

   Please submit a detailed proposal for such a back-up plan by January 31, 2002.

5. Pharmacist *Accutane Dispensing Guide*:

   - The words "as required by law" should be added to the statement "Dispense an Accutane Medication Guide with each Accutane prescription, *as required by law".*
   - Add the color of the Qualification Sticker (yellow) to the Guide.
   - The word "automatic" is not necessary in association with "refills".

6. Bulk Carton Dispensing Instructions for Pharmacists: Ensure that the operational procedure for dispensing is printed on the "permanent" side of the carton, not the part that is torn off in opening. The *Procedure for Pharmacist* should include "No Refills".

7. Produce a patient education video that directly and graphically links serious birth defects to Accutane exposure, similar to the video for thalidomide produced by Celgene. This should be submitted as a labeling supplement within 3 months.

8. Both of the *Informed Consent/Patient Agreements* must meet the requirements for Medication Guide

minimum font size.

9. For educational brochures (in addition to edits as shown in documents):

   - Remove all acne efficacy photographs
   - Insert, where appropriate, information about the newly approved hormonal contraceptive ring device
   - Add Table of Contents to the *Guide to Best Practices* and *Preventing Pregnancy: Guide to Contraception*
   - On the front of the patient guides (*Be Smart, Be Safe, Be Sure*), place a prominent space clearly indicating that the prescriber should write in the phone number that their patient should call if they have questions or problems on Accutane. This will help alleviate semantic confusion about who is the "doctor", the "provider", the "prescriber", etc.
   - *Be Smart, Be Safe, Be Sure* for men:
     - The cover should delete reference to pregnancy prevention and the logo for birth defects.
     - The Boxed Warning for women on the second page should be deleted.
     - The "Additional Information" for men should be presented before the "brochure" for all patients (*Important Information Concerning Your Treatment with Accutane*). The wording for "Additional Information" should be as appended (replace what was submitted).

10. Regarding the Prescription Compliance Survey:

    - For each survey wave, you should provide an assessment of the representativeness of the pharmacies surveyed compared with all dispensing pharmacies in the SK & A pharmacy universe. Pharmacy characteristics that are anticipated to affect compliance with the use of Accutane qualification stickers, and which should be critically evaluated, include store type, geographical region, population density served, and total prescription volume.

    - For each survey wave, you should expand the field audits that will be conducted to directly validate the accuracy with which Accutane prescriptions are collected and characterized by pharmacies. We recommend a 10% audit, at a minimum, of the completeness and accuracy of survey responses for each pharmacy stratum, as characterized by store type, geographical region, population density served, and total prescription volume.

    - You should clarify that pharmacists will report on sticker use for a month prior to recruitment in a survey, and that pharmacists who have declined to participate will not be recontacted.

11. Regarding the Accutane Survey (conducted by the Slone Epidemiology Unit):

    - A precise method for calculating enrollment in the Slone Survey must be specified. Methods for calculating both the numerator (respondents providing useful survey information) and the denominator (all female Accutane users in the U.S.) are necessary.

    - You are directed to seek a means of assessing representativeness of the Slone Survey that is better than the comparison of survey respondents to a managed care population (MCP), unless it can be documented that the MCP is nationally representative and reliably captures both

pregnancies and contraceptive practices/prescriptions. You should explore comparisons of demographic data obtained by linking census data to the zip codes of Accutane users and Slone Survey respondents.

- Since women may complete 2 or more versions of the DAT3 questionnaire, analyses of this survey wave should include subanalyses of women responding more than once and provide a clear *a priori* plan for handling conflicting data should they occur among multiple DAT3 responses by individual respondents.

12. The proposed Independent Chart Review is not acceptable.

13. You should submit a comprehensive report on the SMART Program, including information on the metrics achieved during the first full year of implementation of Qualification Stickers (April 10, 2002 through April 9, 2003), to FDA on or before June 30, 2003. FDA plans to convene a meeting with the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC), including, teratologists, women's health practitioners, dermatologists, pediatricians, and medical ethicists, to discuss survey findings and measures of the program's overall effectiveness. Changes to the S.M.A.R.T. program may be required, including a mandatory registry program.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

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

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA regarding post-marketing reporting of adverse drug experience set forth under 21 CFR 314.80 and 314.81. As indicated in the FDA letter of October 27, 2000, to meet your postmarketing reporting requirement under 21 CFR 314.80 (c) and 21 CFR 314.81 (b), you should submit the following:

- All pregnancy exposures, regardless of the outcomes, as serious, labeled event reports in your annual periodic report;

- A summary and discussion of the clinical significance of the pregnancy exposures in the same annual periodic report and

- All reports of fetal abnormalities as 15-day expedited reports.

In addition, you should include a status summary of each condition in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these conditions for approval must be prominently labeled.

You may request a meeting with the staff of the Office of Postmarketing Drug Risk Assessment to discuss the details of your responses to conditions 10 and 11 outlined in this letter.

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

Sincerely,

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

# ACCUTANE® QUALIFICATION STICKER

_____ Female _____ Male

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

QS XXXXXXXX DEA # ABXXXXXXX

**Pharmacist:**

- **Dispense within 7 days of qualification date**
- **No more than 30-day supply ONLY**
- **No refills allowed**

# *System to Manage Accutane Related Teratogenicity*™ (S.M.A.R.T.™)
# *Letter of Understanding for Prescribers*

The *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) allows Accutane® (isotretinoin) prescribers to be in compliance with the approved Accutane package insert. I acknowledge that by completing this form I demonstrate my understanding of the safe and effective use of Accutane as described in the Checklist below, in the Accutane package insert, and in educational resources provided with this Letter.

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

I understand that use of the yellow self-adhesive Accutane Qualification Sticker means that a female patient is qualified to receive an Accutane prescription, as defined in the CONTRAINDICATIONS AND WARNINGS of the approved labeling. Specifically, she:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month prior to the female patient receiving each prescription.
- Must have selected and have committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month after discontinuing Accutane therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.
- Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.
- Must have been informed of the purpose and importance of participating in the Accutane Survey and given the opportunity to enroll (see PRECAUTIONS).

See complete product information, including CONTRAINDICATIONS AND WARNINGS, in the attached package insert.

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To participate in S.M.A.R.T. and obtain the yellow self-adhesive Accutane Qualification Stickers, please complete the information below and return it to Roche in the preaddressed envelope provided.

**Prescriber name (Last)** _____ **(First)** _____ **(MI)** _____

**DEA number** _____ **Last four digits of Social Security number** _____

**Prescriber address** _____

**City** _____

**State** _____

**Zip code** _____

**Telephone** _____

**Fax** _____

**Prescriber signature** _____ **Date** _____

Information provided above will be held by a third party associated with Roche for the sole purpose of distributing Accutane Qualification Stickers. If you have any questions, please contact the S.M.A.R.T. Program staff at 1-800-93-ROCHE.

Roche Pharmaceuticals

18-004-100-034-1103

# REPRODUCTION OF THIS QUESTIONNAIRE IS PROHIBITED WITHOUT WRITTEN PERMISSION FROM HOFFMANN-LA ROCHE

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**DAT1 Questionnaire (During and After Treatment Arm)**
**For enrollments received on forms provided by doctors**

***Please complete this survey using a black or blue pen or a No. 2 pencil. Fill in selected circles completely.***

A. Have you filled your acne medication prescription?

○1 Yes ○2 No → IF NO, GO TO THE NEXT PAGE AND BEGIN WITH QUESTION 1

Pictures of the three strengths of Accutane® pills are shown here. Each pill has the words "Accutane®" and "Roche" stamped on it. If your pill has the words "Accutane®" and "Roche" stamped on it, please fill in the circle 1 (Yes) for Question B.

If your pill does not have the "Accutane®" and "Roche" stamp on it, please fill in the circle 2 (No) for Question B. This will indicate that you are taking generic isotretinoin.


B. Is your medication Accutane® ?

○1 Yes IF YES, please fill in the Lot number _____ (*Lot number is printed on the bottom edge of the back of your blister pack of Accutane® pills*).

IF YES, PLEASE GO TO THE NEXT PAGE AND BEGIN WITH QUESTION 1

○2 No IF NO, please print the generic isotretinoin drug name: _____ *(Found on the prescription label).*

**Please note that the questions on the following pages ask about your use of the drug Accutane®. Since you are taking generic isotretinoin, please answer the questions on the following pages as if "Accutane®" means the drug that you are taking.**

○3 Not sure

**PLEASE GO TO THE NEXT PAGE AND BEGIN WITH QUESTION 1.**

**This page is intentionally left blank.**

111

1. Did you take any of the Accutane® prescribed by your doctor?
   - ○1 Yes - Date started: ☐☐☐☐☐☐☐☐ (M M D D Y Y Y Y)
   - ○2 Not yet* - Expected start date: ☐☐☐☐☐☐☐☐ (M M D D Y Y Y Y)
   - ○3 No, I never took any. Please explain below and then skip to Question 40.

   _____

2. On what date did you receive your first Accutane® prescription from your doctor or the doctor's office?
   ☐☐☐☐☐☐☐☐ (M M D D Y Y Y Y)
3. On what date did you fill your first Accutane® prescription? *This information can be found on your prescription label.*
   ☐☐☐☐☐☐☐☐ (M M D D Y Y Y Y)
4. Was there a yellow "Accutane® Qualification Sticker" on either the back or the front of your Accutane® prescription?
   - ○1 Yes.
   - ○2 I haven't received my prescription yet.
   - ○3 Someone else obtained and filled my prescription for me.
   - ○4 I didn't see the prescription. Please explain: _____
   - ○5 I saw the prescription and it didn't have a sticker.
5. When you filled any of your Accutane® prescriptions, did you receive a one-page document printed on both sides (8.5 by 11 inches in size) called the "Medication Guide"?
   ○1 Yes ○2 No ○3 Not sure
6. Did your doctor or anyone in the doctor's office encourage you to enroll in this Survey?
   ○1 Yes ○2 No → IF NO, SKIP TO QUESTION 7

   IF YES, please fill in one circle next to the number on the scale below that best describes how much you were encouraged to enroll:

   1 ○ 2 ○ 3 ○ 4 ○ 5 ○
   Encouraged a little ◄——————————► Encouraged a lot
7. Where did you find the enrollment form?
   - ○1 My doctor or someone in the doctor's office pointed it out to me
   - ○2 I found it on my own in the Be Smart | Be Safe | Be Sure notebook (a pink spiral notebook given to you by your doctor or someone in your doctor's office).

* If you have not yet started your Accutane® treatment, please do not answer questions 2-3, 24-27, 30-32, 36-38.

***Please turn this page over and continue on the other side.***

8. Did your doctor or anyone in the doctor's office tell you that you would also receive a Survey enrollment form in your Accutane® medication package?
   ○1 Yes ○2 No ○3 Not sure

9. How old were you when your acne first developed?
   ☐☐ years old

10. How old were you the first time you saw a doctor for acne?
    ☐☐ years old

11. Before starting Accutane®, did you ever use any of the following treatments for acne? *(Fill in all circles that apply.)*

| | |
|---|---|
| ○1 Antibiotics taken by mouth | ○2 Antibiotics applied to skin |
| ○3 Ortho Tri-cyclen | ○4 Benzoyl peroxide |
| ○5 Vitamin A taken by mouth | ○6 Differin |
| ○7 Other medicines taken by mouth: specify in box below | ○8 Retin-A / Retin-A Micro |
| | ○9 Other: specify in box below |

| | |
|---|---|
| | |

12. Is this your first Accutane® treatment?
    ○1 Yes → IF YES, SKIP TO QUESTION 13 ○2 No
    IF NO, how many other Accutane® treatments have you had?
    ○1 1 ○2 2-3 ○3 4 or more

13. What might Accutane® do if it is taken **during pregnancy**? *(Fill in all circles that apply.)*
    ○1 Cause birth defects
    ○2 Cause miscarriage
    ○3 None of the above

14. Did your doctor tell you that it is important not to become pregnant while taking Accutane®?
    ○1 Yes ○2 No

15. Did you receive and read any of the following materials about Accutane®? *(Fill in all circles that apply.)*

| | RECEIVED? | | READ? | |
|---|---|---|---|---|
| Be Smart \| Be Safe \| Be Sure pink spiral notebook | ○1 Yes | ○2 No | ○1 Yes | ○2 No |
| Contraception Knowledge Self-Assessment | ○1 Yes | ○2 No | ○1 Yes | ○2 No |
| A Guide to Contraception | ○1 Yes | ○2 No | ○1 Yes | ○2 No |
| Other materials | ○1 Yes | ○2 No | ○1 Yes | ○2 No |

16. Did you watch the video, *Be Prepared, Be Protected*?
    ○1 Yes ○2 No ○3 Not sure

17. Do you know about the Accutane® InfoLine, the toll-free telephone Accutane® information line?
○1 Yes ○2 No ○3 Not sure → IF NO, SKIP TO QUESTION 18

IF YES, did you call the Accutane® InfoLine?
○1 Yes ○2 No → IF NO, SKIP TO QUESTION 18

IF YES, what language did you request?

| | | |
|---|---|---|
| ○1 English | ○2 Russian | ○3 Japanese |
| ○4 French | ○5 Korean | ○6 Italian |
| ○7 Vietnamese | ○8 Portuguese | ○9 Polish |
| ○10 Spanish | ○11 German | ○12 Chinese |

18. Do you know about the toll-free Confidential Contraception Counseling Line?
○1 Yes ○2 No ○3 Not sure → IF NO, SKIP TO QUESTION 19

IF YES, did you call the Confidential Contraception Counseling Line?
○1 Yes ○2 No → IF NO, SKIP TO QUESTION 19

IF YES, please fill in one circle next to the number on the scale below that best describes how helpful you found this call.

○1 ○2 ○3 ○4 ○5
Not at all helpful ◄——————————► Extremely helpful

19. Did your doctor or anyone in the doctor's office discuss contraception with you?
○1 Yes ○2 No ○3 Not sure → IF NO, SKIP TO QUESTION 20

IF YES, please fill in one circle next to the number on the scale below that best describes how helpful you found this discussion.

○1 ○2 ○3 ○4 ○5
Not at all helpful ◄——————————► Extremely helpful

Did you change your contraceptive method or practices as a result of this discussion?
○1 Yes ○2 No

***Please turn this page over and continue on the other side.***

20. Did your doctor or anyone in the doctor's office offer to refer you to another health care provider for contraceptive counseling?

○1 Yes ○2 No ○3 Not sure → IF NO, SKIP TO QUESTION 21

IF YES, did you see another health care provider for contraceptive counseling?

○1 Yes ○2 No ○3 Not sure → IF NO, SKIP TO QUESTION 21

IF YES, who was this health care provider?

○1 A doctor specializing in obstetrics and gynecology
○2 A family practice doctor
○3 A dermatologist
○4 A nurse practitioner
○5 A physician's assistant
○6 Another type of doctor; please print: _____
○7 Other; please print: _____

Please fill in one circle next to the number on the scale below that best describes how helpful you found this counseling.

○1 ○2 ○3 ○4 ○5

Not at all helpful ◄——————————► Extremely helpful

Did you change your contraceptive method as a result of this discussion?

○1 Yes ○2 No

21. Did your doctor or anyone in the doctor's office mention anything about emergency contraception (the "morning after pill")?

○1 Yes ○2 No ○3 Not sure

22. Did you read about emergency contraception (the "morning after pill") in the Be Smart | Be Safe | Be Sure notebook (a pink spiral notebook given to you by your doctor or someone in your doctor's office)?

○1 Yes ○2 No ○3 Not sure

23. Did your doctor or anyone in your doctor's office ask you to sign consent forms that were in the Be Smart | Be Safe | Be Sure notebook (a pink spiral notebook given to you by your doctor or someone in your doctor's office)?

○1 Yes, I signed 2 forms ○2 Yes, I signed 1 form ○3 No, I didn't sign any ○4 I'm not sure

*The next questions concern pregnancy tests in the 4 weeks before starting Accutane®. Like all the information you provide, your answers will be kept strictly confidential and are extremely important to the Survey.*

24. How many pregnancy tests did you have *in a laboratory or doctor's office* during the 4 weeks before you began taking Accutane®?

☐☐ Blood pregnancy tests
☐☐ Urine pregnancy tests
☐☐ Unknown type of pregnancy test

25. How many urine pregnancy tests *did you do at home* during the 4 weeks before you began taking Accutane®?
    ☐☐ → How many of these test results did you report to your doctor? ☐☐

26. What was the date of the last pregnancy test you had *before starting* Accutane®?
    ☐☐☐☐☐☐☐☐
    M M D D Y Y Y Y

27. Did you have a menstrual period in the 4 weeks before you began taking Accutane®?
    ○1 Yes ○2 No ○3 Not sure → IF NO/NOT SURE, SKIP TO QUESTION 28
    IF YES, on what date did that menstrual period begin? ☐☐☐☐☐☐☐☐
    M M D D Y Y Y Y
    During that menstrual period did you have a pregnancy test?
    ○1 Yes ○2 No → IF NO, SKIP TO QUESTION 28
    IF YES, on what day of your menstrual period did you have that pregnancy test?
    ○1 The first day ○2 The second day ○3 The third day
    ○4 The fourth day ○5 The fifth day ○6 The sixth day or later

28. Did your doctor or anyone in the doctor's office give you a urine pregnancy test kit to use at home?
    ○1 Yes ○2 No

*The following questions deal with sensitive issues. However, they are necessary to help us interpret the other information you provide. Remember that all your answers will be kept strictly confidential.*

29. Have you ever had sexual intercourse with a male partner?
    ○1 Yes ○2 No → IF NO, SKIP TO QUESTION 33

30. In the 3 months before you started taking Accutane®, did you have sexual intercourse with a male partner?
    ○1 Yes ○2 No

31. Since you started taking Accutane®, have you had sexual intercourse with a male partner?
    ○1 Yes ○2 No → IF NO, SKIP TO QUESTION 33

32. Do any of the following apply to that male partner?
    ○1 He was infertile because of a vasectomy. (Date of vasectomy: ☐☐ ☐☐)
    M M Y Y
    ○2 He was infertile for other reasons.

33. Do any of the following apply to you?
    ○1 I have had a hysterectomy.
    ○2 I have completed menopause.
    ○3 I have had a tubal ligation. Date: ☐☐ ☐☐
    ○4 I am infertile. For how many years? ☐☐
    ○5 None of these apply.

34. Are you currently using any method(s) of birth control?
    ○1 Yes ○2 No → IF NO, SKIP TO QUESTION 36

***Please turn this page over and continue on the other side.***

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35. What method(s) of birth control are you **currently** using?

**Tell us how long you have been using each current method.**

| CURRENT METHOD(S) | 1 mo. or less | 2 mos. | 3 mos. | 4 mos. | 5 mos. | 6 mos. | 7 mos. | 8 mos. | 9 mos. | 10 mos. | 11 mos. | 12 mos. | Over 1 year |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ○ Birth control pills | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Condoms (rubbers) | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ "Reality" female condoms | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Depo-Provera injections | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Diaphragm (with or without cream/jelly) | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ IUD | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Lunelle injections | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Norplant implant | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Spermicide : film foam suppositories cream | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Tubal ligation (tubes tied) | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Vasectomy | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| ○ Other - specify in box below: | ○1 | ○2 | ○3 | ○4 | ○5 | ○6 | ○7 | ○8 | ○9 | ○10 | ○11 | ○12 | ○13 |
| | | | | | | | | | | | | | |

36. Since you started taking Accutane®, have you used emergency contraception (the "morning after pill")?
○1 Yes ○2 No

37. Have you been pregnant at any time since you first started taking Accutane? *Please include current pregnancies as well as abortions, miscarriages, ectopic/tubal pregnancies, etc.*
○1 Yes ○2 No ○3 Not sure

38. Are you still taking Accutane®? ○1 Yes ○2 No When did you stop? ☐☐☐☐☐☐☐☐
M M D D Y Y Y Y

39. Because it is important to the accuracy of the Survey that we complete follow-up on all women who enroll, it will be helpful if you can provide the names of 2 people we may contact if we have difficulty locating you at a later date.

Name: _____ Name: _____

Address: _____ Address: _____

_____ _____

City: _____ City: _____

State: ☐☐ Zip: ☐☐☐☐☐ State: ☐☐ Zip: ☐☐☐☐☐

Telephone: ☐☐☐ ☐☐☐ ☐☐☐☐ Telephone: ☐☐☐ ☐☐☐ ☐☐☐☐

40. Please provide the date on which you are completing this form: ☐☐☐☐☐☐☐☐
M M D D Y Y Y Y




Timing of Exposure to Accutane Therapy Relative to Pregnancy

| | Known Therapy Start Date | | Unknown Therapy Start Date | |
|---|---|---|---|---|
| | SMART (N=94) | Pre-SMART (N=93) | SMART (N=89) | Pre-SMART (N=56) |
| Pregnant when Accutane started | 10 (10.6%) | 16 (17.2%) | 14 (15.7%) | 12 (21.4%) |
| Taking Accutane when pregnancy occurred | 80 (85.1%) | 76 (81.7%) | 53 (59.6%) | 44 (78.6%) |
| Unknown | 4 (4.3%) | 1 (1.1%) | 22 (24.7%) | 0 |

**Timing of Exposure to Accutane versus Pregnancy Outcome – S.M.A.R.T. Pregnancies with Known Therapy Start Dates**

| | Pregnancy Outcome | | | | | |
|---|---|---|---|---|---|---|
| | Delivery N | Lost to follow-up N | Ongoing N | Spontaneous abortion N | Therapeutic abortion N | Unknown N |
| Pregnant when Accutane started | - | 8 | 1 | - | - | 1 |
| Taking Accutane when pregnancy occurred | 6 | 16 | 14 | 2 | 33 | 9 |
| Unknown | - | 3 | - | - | - | 1 |
| Total | 6 | 27 | 15 | 2 | 33 | 11 |

**Timing of Exposure to Accutane versus Pregnancy Outcome – S.M.A.R.T. Pregnancies with Unknown Therapy Start Dates**

| | Pregnancy Outcome | | | | | |
|---|---|---|---|---|---|---|
| | Delivery N | Lost to follow-up N | Ongoing N | Spontaneous abortion N | Therapeutic abortion N | Unknown N |
| Pregnant when Accutane started | 1 | 8 | 1 | - | 4 | - |
| Taking Accutane when pregnancy occurred | 12 | 32 | 1 | - | 7 | 1 |
| Unknown | 1 | 19 | - | - | 1 | 1 |
| Total* | 14 | 59 | 2 | - | 12 | 2 |