



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

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,

{See appended electronic signature page}

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

Enclosure

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

/s/

Jonathan Wilkin
10/30/01 03:56:10 PM

ACCUTANE® (isotretinoin)



1

2 ACCUTANE®
3 (isotretinoin)
4 CAPSULES

5 CAUSES BIRTH DEFECTS



6

7 AVOID PREGNANCY

8

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

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

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

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

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

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

36 **Accutane must be prescribed under the *System to Manage Accutane Related***

37 ***Teratogenicity™(S.M.A.R.T.™)***

38 **To prescribe Accutane, the prescriber must obtain a supply of yellow self-adhesive**

39 **Accutane Qualification Stickers. To obtain these stickers:**

- 40 **1) read the booklet entitled *System to Manage Accutane Related Teratogenicity™***
- 41 ***(S.M.A.R.T.™ Guide to Best Practices)***
- 42 **2) sign and return the completed *S.M.A.R.T. Letter of Understanding* containing the**
- 43 **following Prescriber Checklist:**
- 44 • **I know the risk and severity of fetal injury/birth defects from Accutane**
- 45 • **I know how to diagnose and treat the various presentations of acne**
- 46 • **I know the risk factors for unplanned pregnancy and the effective measures for**
- 47 **avoidance of unplanned pregnancy**
- 48 • **It is the informed patient's responsibility to avoid pregnancy during Accutane**
- 49 **therapy and for a month after stopping Accutane. To help patients have the**
- 50 **knowledge and tools to do so: before beginning treatment of female patients with**
- 51 **Accutane I will refer for expert, detailed pregnancy prevention counseling and**
- 52 **prescribing, reimbursed by the manufacturer, OR I have the expertise to**
- 53 **perform this function and elect to do so**
- 54 • **I understand, and will properly use throughout the Accutane treatment course,**
- 55 **the S.M.A.R.T. procedures for Accutane, including monthly pregnancy**
- 56 **avoidance counseling, pregnancy testing and use of Accutane Qualification**
- 57 **Stickers**
- 58
- 59 **3) To use the yellow self-adhesive Accutane Qualification Sticker: Accutane should**
- 60 **not be prescribed or dispensed to any patient (male or female) without a yellow**
- 61 **self-adhesive Accutane Qualification Sticker.**

62 **For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies**

63 **that she:**

- 64 • **Must have had two negative urine or serum pregnancy tests with a sensitivity of**
- 65 **at least 25 mIU/mL before receiving the initial Accutane prescription. The first**

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66 test, (a screening test) is obtained by the prescriber when the decision is made to
67 pursue qualification of the patient for Accutane. The second pregnancy test, (a
68 confirmation test) should be done during the first five days of the menstrual
69 period immediately preceding the beginning of Accutane therapy. For patients
70 with amenorrhea, the second test should be done at least 11 days after the last
71 act of unprotected sexual intercourse (without using 2 effective forms of
72 contraception). Each month of therapy, the patient must have a negative result
73 from a urine or serum pregnancy test. A pregnancy test must be repeated every
74 month prior to the female patient receiving each prescription. The manufacturer
75 will make available urine pregnancy test kits for female Accutane patients for
76 the initial, second and monthly testing during therapy.

- 77 • **Must** have selected and has committed to use two forms of effective
78 contraception simultaneously, at least one of which must be a primary form,
79 unless absolute abstinence is the chosen method, or the patient has undergone a
80 hysterectomy. Patients must use two forms of effective contraception for at least
81 one month prior to initiation of Accutane therapy, during Accutane therapy, and
82 for one month after discontinuing Accutane therapy. Counseling about
83 contraception and behaviors associated with an increased risk of pregnancy
84 must be repeated on a monthly basis.

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

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

101 **Prescribers are advised to consult the package insert of any medication**
102 **administered concomitantly with hormonal contraceptives, since some medications**
103 **may decrease the effectiveness of these birth control products. Patients should be**
104 **prospectively cautioned not to self-medicate with the herbal supplement St. John's**
105 **Wort because a possible interaction has been suggested with hormonal**
106 **contraceptives based on reports of breakthrough bleeding on oral contraceptives**

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107 shortly after starting St. John's Wort. Pregnancies have been reported by users of
108 combined hormonal contraceptives who also used some form of St. John's Wort.
109 (see PRECAUTIONS)

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

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

118 These yellow self-adhesive Accutane Qualification Stickers should also be used for
119 male patients: check off the "male" gender box without checking the qualification
120 statement.

121 If a pregnancy does occur during treatment of a woman with Accutane, the
122 prescriber and patient should discuss the desirability of continuing the pregnancy.
123 Prescribers are strongly encouraged to report all cases of pregnancy to Roche @ 1-
124 800-526-6367 where a Roche Pregnancy Prevention Program Specialist will be
125 available to discuss Roche pregnancy information, or prescribers may contact the
126 Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

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

134 **INFORMATION FOR PHARMACISTS:**

135 **ACCUTANE MUST ONLY BE DISPENSED:**

- 136 • **IN NO MORE THAN A 1-MONTH SUPPLY**
- 137 • **ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A**
138 **YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- 139 • **WRITTEN WITHIN THE PREVIOUS 7 DAYS**

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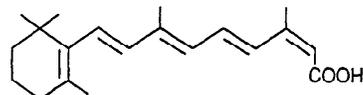
140 • REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-
141 ADHESIVE ACCUTANE QUALIFICATION STICKER

142 • NO TELEPHONE OR COMPUTERIZED PRESCRIPTIONS ARE
143 PERMITTED.

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

148 **DESCRIPTION:** Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and
149 40-mg soft gelatin capsules for oral administration. Each capsule contains beeswax,
150 butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes,
151 hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and
152 parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red)
153 and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium
154 dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

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



159 **CLINICAL PHARMACOLOGY:** Isotretinoin is a retinoid, which when administered
160 in pharmacologic dosages of 0.5 to 2.0 mg/kg/day, inhibits sebaceous gland function and
161 keratinization. The exact mechanism of action of Accutane is unknown.

162 **Nodular Acne:** Clinical improvement in nodular acne patients occurs in association with
163 a reduction in sebum secretion. The decrease in sebum secretion is temporary and is
164 related to the dose and duration of treatment with Accutane, and reflects a reduction in
165 sebaceous gland size and an inhibition of sebaceous gland differentiation.¹

166 **Pharmacokinetics: Absorption:** Oral absorption of isotretinoin is optimal when taken
167 with food or milk. After administration of a single 80-mg oral dose (two 40-mg capsules)
168 of isotretinoin to 15 healthy male subjects, maximum blood concentrations ranged from
169 167 to 459 ng/mL (mean 256 ng/mL) and were achieved in 1 to 6 hours (mean 3.2 hours).
170 The oral absorption of isotretinoin is consistent with first-order kinetics and can be
171 described with a linear two-compartment model. Nodular acne does not alter the
172 absorption of the drug: In a 27-day study of isotretinoin in 10 male patients with nodular

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173 acne treated with an oral dose of 40 mg bid, the mean peak concentration ranged from
174 98 ng/mL to 535 ng/mL (mean 262 ng/mL) and occurred at 2 to 4 hours after
175 administration (mean 2.9 hours). In these patients, the mean \pm SD minimum steady-state
176 blood concentration of isotretinoin was 160 ± 19 ng/mL. The terminal elimination half-
177 life was consistent with that observed in normal subjects.

178 *Distribution:* Isotretinoin is more than 99.9% bound to plasma proteins, primarily
179 albumin.

180 *Metabolism:* After oral administration of isotretinoin, 4-*oxo*-isotretinoin is the major
181 metabolite identified in the blood. Maximum concentrations of 4-*oxo*-isotretinoin (87 to
182 399 ng/mL) were achieved at 6 to 20 hours after oral administration of two 40-mg
183 capsules; the blood concentration of the major metabolite generally exceeded that of
184 isotretinoin after 6 hours. Isotretinoin also undergoes isomerization to the all-trans-
185 isomer, tretinoin, which is then metabolized to its corresponding 4-*oxo*-metabolite; both
186 have been detected. Both parent compound and metabolites are further metabolized into
187 conjugates which are excreted.

188 *Elimination:* Following administration of an 80-mg liquid suspension oral dose of ^{14}C -
189 isotretinoin, ^{14}C -activity in blood declined with a half-life of 90 hours. The metabolites of
190 isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively
191 equal amounts (total of 65% to 83%). The terminal elimination half-life of isotretinoin
192 ranges from 10 to 20 hours. The mean elimination half-life of 4-*oxo*-isotretinoin is 25
193 hours (range 17 to 50 hours). After both single and multiple doses, the accumulation ratio
194 of 4-*oxo*-isotretinoin to parent compound is 3 to 3.5.

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

204
205 A single course of therapy for 15 to 20 weeks has been shown to result in complete and
206 prolonged remission of disease in many patients.^{1,3,4} If a second course of therapy is
207 needed, it should not be initiated until at least 8 weeks after completion of the first
208 course, because experience has shown that patients may continue to improve while off
209 Accutane. The optimal interval before retreatment has not been defined for patients who
210 have not completed skeletal growth (see WARNINGS: *Skeletal: Hyperostosis* and
211 *Premature Epiphyseal Closure*).

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212 **CONTRAINDICATIONS: Pregnancy: Category X. See boxed**
213 **CONTRAINDICATIONS AND WARNINGS.**

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

218 **WARNINGS: Psychiatric Disorders:** Accutane may cause depression, psychosis and,
219 rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane
220 therapy may be insufficient; further evaluation may be necessary. No mechanism of
221 action has been established for these events (see **ADVERSE REACTIONS:**
222 *Psychiatric*).

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

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

235 *Lipids:* Elevations of serum triglycerides have been reported in patients treated with
236 Accutane. Marked elevations of serum triglycerides in excess of 800 mg/dL were
237 reported in approximately 25% of patients receiving Accutane in clinical trials. In
238 addition, approximately 15% developed a decrease in high-density lipoproteins and about
239 7% showed an increase in cholesterol levels. In clinical trials, the effects on
240 triglycerides, HDL, and cholesterol were reversible upon cessation of Accutane therapy.
241 Some patients have been able to reverse triglyceride elevation by reduction in weight,
242 restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane.⁵

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

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250 The cardiovascular consequences of hypertriglyceridemia associated with Accutane are
251 unknown. *Animal Studies:* In rats given 8 or 32 mg/kg/day of isotretinoin (0.7 or 2.7
252 times the maximum clinical dose after normalization for total body surface area) for 18
253 months or longer, the incidences of focal calcification, fibrosis and inflammation of the
254 myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic
255 calcification of the gastric mucosa were greater than in control rats of similar age. Focal
256 endocardial and myocardial calcifications associated with calcification of the coronary
257 arteries were observed in two dogs after approximately 6 to 7 months of treatment with
258 isotretinoin at a dosage of 60 to 120 mg/kg/day (15 to 30 times the maximum clinical
259 dose, respectively, after normalization for total body surface area).

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

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

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

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

286 *Premature Epiphyseal Closure:* There are spontaneous reports of premature epiphyseal
287 closure in acne patients receiving recommended doses, but it is not known if there is a
288 causal relationship with Accutane. In clinical trials for disorders of keratinization with a
289 mean dose of 2.24 mg/kg/day, two children showed x-ray findings suggestive of

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290 premature epiphyseal closure. The skeletal effects of multiple Accutane treatment courses
291 for acne are unknown.

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

295 **Corneal Opacities:** Corneal opacities have occurred in patients receiving Accutane for
296 acne and more frequently when higher drug dosages were used in patients with disorders
297 of keratinization. The corneal opacities that have been observed in clinical trial patients
298 treated with Accutane have either completely resolved or were resolving at follow-up 6 to
299 7 weeks after discontinuation of the drug (see ADVERSE REACTIONS: *Special Senses*).

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

305 **PRECAUTIONS:** The Accutane pregnancy prevention risk management program
306 consists of the *System to Manage Accutane Related Teratogenicity (S.M.A.R.T.)* and the
307 Accutane Pregnancy Prevention Program® (PPP). S.M.A.R.T. should be followed for
308 prescribing Accutane with the goal of preventing fetal exposure to isotretinoin. It consists
309 of: 1) reading the booklet entitled *System to Manage Accutane Related Teratogenicity*
310 *(S.M.A.R.T.) Guide to Best Practices*, 2) signing and returning the completed *S.M.A.R.T.*
311 *Letter of Understanding* containing the Prescriber Checklist, 3) a yellow self-adhesive
312 Accutane Qualification Sticker to be affixed to the prescription page. In addition, the
313 patient educational material, *Be Smart, Be Safe, Be Sure*, in the Accutane Pregnancy
314 Prevention Program® (PPP) should be used with each patient.

315 The following further describes each component:

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

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

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

336 3) The yellow self-adhesive Accutane Qualification Sticker is used as documentation
337 that the prescriber has qualified the female patient according to the qualification
338 criteria (see boxed CONTRAINDICATIONS AND WARNINGS.)

339 4) *Accutane Pregnancy Prevention Program* (PPP) is a systematic approach to
340 comprehensive patient education about their responsibilities and includes education
341 for contraception compliance and reinforcement of educational messages. The PPP
342 includes information on the risks and benefits of Accutane which is linked to the
343 Accutane Medication Guide dispensed by pharmacists with each prescription.

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

348 The booklet for male patients also includes information about male reproduction, a
349 warning not to share Accutane with others or to donate blood during Accutane
350 therapy and for 1 month following discontinuation of Accutane.

351 The booklet for female patients also includes a referral program that offers females
352 free contraception counseling, reimbursed by the manufacturer, by a reproductive
353 specialist; a second Patient Information/Consent form concerning birth defects,
354 obtaining her consent to be treated within this agreement; an enrollment form for the
355 Accutane Survey; and a qualification checklist affirming the conditions under which
356 female patients may receive Accutane. In addition, there is information on the types
357 of contraceptive methods, the selection and use of appropriate, effective
358 contraception, and the rates of possible contraceptive failure; a toll-free contraception
359 counseling line; and a video about the most common reasons for unplanned
360 pregnancies.

361 ***Information for Patients and Prescribers:***

- 362 • Patients should be instructed to read the Medication Guide supplied as required by
363 law when Accutane is dispensed. The complete text of the Medication Guide is

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364 reprinted at the end of this document. For additional information, patients should also
365 read the Patient Information Brochure, "*Important Information Concerning Your*
366 *Treatment with Accutane® (isotretinoin)*". All patients should sign the Informed
367 Consent/Patient Agreement.

368

369 • Females of childbearing potential should be instructed that they must not be pregnant
370 when Accutane therapy is initiated, and that they should use two forms of effective
371 contraception one month before starting Accutane, while taking Accutane, and for 1
372 month after Accutane has been stopped. They should also sign a consent form prior to
373 beginning Accutane therapy. They should be given an opportunity to enroll in the
374 Accutane Survey and to review the patient videotape provided by the manufacturer to
375 the prescriber. It includes information about contraception, the most common reasons
376 that contraception fails, and the importance of using two forms of effective
377 contraception when taking teratogenic drugs. Female patients should be seen by their
378 prescribers monthly and have a urine or serum pregnancy test performed each month
379 during treatment to confirm negative pregnancy status before another Accutane
380 prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).

381 • Accutane is found in the semen of male patients taking Accutane, but the amount
382 delivered to a female partner would be about 1 million times lower than an oral dose
383 of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown,
384 20 years of post-marketing reports include 4 with isolated defects compatible with
385 features of retinoid exposed fetuses. None of these cases had the combination of
386 malformations characteristic of retinoid exposure, and all had other possible
387 explanations for the defects observed.

388 • Patients may report mental health problems or family history of psychiatric disorders.
389 These reports should be discussed with the patient and/or the patient's family. A
390 referral to a mental health professional may be necessary. The physician should
391 consider whether or not Accutane therapy is appropriate in this setting. (see
392 WARNINGS: *Psychiatric*)

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

395 • Patients should not donate blood during therapy and for 1 month following
396 discontinuance of the drug because the blood might be given to a pregnant woman
397 whose fetus must not be exposed to Accutane.

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

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- 400 • Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should
401 be avoided during Accutane therapy and for at least 6 months thereafter due to the
402 possibility of scarring (see ADVERSE REACTIONS: *Skin and Appendages*).
- 403 • Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- 404 • Patients should be informed that they may experience decreased tolerance to contact
405 lenses during and after therapy.
- 406 • Patients should be informed that approximately 16% of patients treated with
407 Accutane in a clinical trial developed musculoskeletal symptoms (including
408 arthralgia) during treatment. In general, these symptoms were mild to moderate, but
409 occasionally required discontinuation of the drug. Transient pain in the chest has been
410 reported less frequently. In the clinical trial, these symptoms generally cleared rapidly
411 after discontinuation of Accutane, but in some cases persisted (see ADVERSE
412 REACTIONS: *Musculoskeletal*).
- 413 • Neutropenia and rare cases of agranulocytosis have been reported. Accutane should
414 be discontinued if clinically significant decreases in white cell counts occur.
- 415 *Hypersensitivity:* Anaphylactic reactions and other allergic reactions have been reported.
416 Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura
417 (bruises and red patches) of the extremities and extracutaneous involvement (including
418 renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy
419 and appropriate medical management.
- 420 *Drug Interactions:*
- 421 • Because of the relationship of Accutane to vitamin A, patients should be advised
422 against taking vitamin supplements containing vitamin A to avoid additive toxic
423 effects.
- 424 • Concomitant treatment with Accutane and tetracyclines should be avoided because
425 Accutane use has been associated with a number of cases of pseudotumor cerebri
426 (benign intracranial hypertension), some of which involved concomitant use of
427 tetracyclines.
- 428 • Micro-dosed progesterone preparations (“minipills” that do not contain an estrogen)
429 may be an inadequate method of contraception during Accutane therapy. Although
430 other hormonal contraceptives are highly effective, there have been reports of
431 pregnancy from women who have used combined oral contraceptives, as well as
432 injectable/implantable contraceptive products. These reports are more frequent for
433 women who use only a single method of contraception. It is not known if hormonal
434 contraceptives differ in their effectiveness when used with Accutane. Therefore, it is
435 critically important for women of childbearing potential to select and commit to use

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436 two forms of effective contraception simultaneously, at least one of which must be a
437 primary form, unless absolute abstinence is the chosen method, or the patient has
438 undergone a hysterectomy (see boxed CONTRAINDICATIONS AND
439 WARNINGS).

440 Prescribers are advised to consult the package insert of medication administered
441 concomitantly with hormonal contraceptives, since some medications may decrease the
442 effectiveness of these birth control products. Accutane use is associated with depression
443 in some patients. (See WARNINGS: *Psychiatric* and ADVERSE REACTIONS:
444 *Psychiatric*) Patients should be prospectively cautioned not to self-medicate with the
445 herbal supplement St. John's Wort because a possible interaction has been suggested with
446 hormonal contraceptives based on reports of breakthrough bleeding on oral
447 contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by
448 users of combined hormonal contraceptives who also used some form of St. John's Wort.
449

450 *Laboratory Tests:*

451 *Pregnancy Test:* Female patients of childbearing potential must have negative results
452 from two urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before
453 receiving the initial Accutane prescription. The first test is obtained by the prescriber
454 when the decision is made to pursue qualification of the patient for Accutane, (a
455 screening test). The second pregnancy test (a confirmation test) should be done during
456 the first five days of the menstrual period immediately preceding the beginning of
457 Accutane therapy. For patients with amenorrhea, the second test should be done at least
458 11 days after the last act of unprotected sexual intercourse (without using 2 effective
459 forms of contraception).

460 Each month of therapy, the patient must have a negative result from a urine or serum
461 pregnancy test. A pregnancy test must be repeated each month prior to the female patient
462 receiving each prescription.
463

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

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

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

477 • *CPK*: Some patients undergoing vigorous physical activity while on Accutane
478 therapy have experienced elevated CPK levels; however, the clinical significance is
479 unknown.

480 *Carcinogenesis, Mutagenesis and Impairment of Fertility*: In male and female Fischer
481 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (0.7 or 2.7 times the
482 maximum clinical dose, respectively, after normalization for total body surface area) for
483 greater than 18 months, there was a dose-related increased incidence of
484 pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia
485 was also increased at the higher dosage in both sexes. The relatively high level of
486 spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an
487 equivocal model for study of this tumor; therefore, the relevance of this tumor to the
488 human population is uncertain.

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

497 In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or
498 parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.2,
499 0.7, or 2.7 times the maximum clinical dose, respectively, after normalization for total
500 body surface area).

501 In dogs, testicular atrophy was noted after treatment with oral isotretinoin for
502 approximately 30 weeks at dosages of 20 or 60 mg/kg/day (5 or 15 times the maximum
503 clinical dose, respectively, after normalization for total body surface area). In general,
504 there was microscopic evidence for appreciable depression of spermatogenesis but some
505 sperm were observed in all testes examined and in no instance were completely atrophic
506 tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under
507 treatment with oral isotretinoin, no significant changes were noted in the count or motility
508 of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving
509 Accutane (isotretinoin) therapy for nodular acne, no significant effects were seen on
510 ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma
511 fructose.

512 ***Pregnancy*: Category X. See boxed CONTRAINDICATIONS AND WARNINGS.**

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- 513 *Nursing Mothers:* It is not known whether this drug is excreted in human milk. Because
514 of the potential for adverse effects, nursing mothers should not receive Accutane.
- 515 **ADVERSE REACTIONS: *Clinical Trials and Postmarketing Surveillance:*** The
516 adverse reactions listed below reflect the experience from investigational studies of
517 Accutane, and the postmarketing experience. The relationship of some of these events to
518 Accutane therapy is unknown. Many of the side effects and adverse reactions seen in
519 patients receiving Accutane are similar to those described in patients taking very high
520 doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal
521 passage, and eyes).
- 522 ***Dose Relationship:*** Cheilitis and hypertriglyceridemia are usually dose related. Most
523 adverse reactions reported in clinical trials were reversible when therapy was
524 discontinued; however, some persisted after cessation of therapy (see WARNINGS and
525 ADVERSE REACTIONS).
- 526 *Body as a Whole:* allergic reactions, including vasculitis, systemic hypersensitivity (see
527 PRECAUTIONS: *Hypersensitivity*), edema, fatigue, lymphadenopathy, weight loss
- 528 *Cardiovascular:* palpitation, tachycardia, vascular thrombotic disease, stroke
- 529 *Endocrine/Metabolic:* hypertriglyceridemia (see WARNINGS: *Lipids*), alterations in
530 blood sugar levels (see PRECAUTIONS: *Laboratory Tests*)
- 531 *Gastrointestinal:* inflammatory bowel disease (see WARNINGS: *Inflammatory Bowel*
532 *Disease*), hepatitis (see WARNINGS: *Hepatotoxicity*), pancreatitis (see WARNINGS:
533 *Lipids*), bleeding and inflammation of the gums, colitis, ileitis, nausea, other nonspecific
534 gastrointestinal symptoms
- 535 *Hematologic:* allergic reactions (see PRECAUTIONS: *Hypersensitivity*), anemia,
536 thrombocytopenia, neutropenia, rare reports of agranulocytosis (see PRECAUTIONS:
537 *Information for Patients and Prescribers*). See PRECAUTIONS: *Laboratory* for other
538 hematological parameters.
- 539 *Musculoskeletal:* skeletal hyperostosis, calcification of tendons and ligaments, premature
540 epiphyseal closure (see WARNINGS: *Skeletal*), mild to moderate musculoskeletal
541 symptoms including arthralgia (see PRECAUTIONS: *Information for Patients and*
542 *Prescribers*), transient pain in the chest (see PRECAUTIONS: *Information for Patients*
543 *and Prescribers*), elevations of CPK (see PRECAUTIONS: *Laboratory Tests*), arthritis,
544 tendonitis, other types of bone abnormalities
- 545 *Neurological:* pseudotumor cerebri (see WARNINGS: *Pseudotumor Cerebri*), dizziness,
546 drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures,
547 stroke, syncope, weakness

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- 548 *Psychiatric:* suicidal ideation, suicide attempts, suicide, depression, psychosis (see
549 **WARNINGS:** *Psychiatric Disorders*), emotional instability
- 550 Of the patients reporting depression, some reported that the depression subsided with
551 discontinuation of therapy and recurred with reinstatement of therapy.
- 552 *Reproductive System:* abnormal menses
- 553 *Respiratory:* bronchospasms (with or without a history of asthma), respiratory infection,
554 voice alteration
- 555 *Skin and Appendages:* acne fulminans, alopecia (which in some cases persists), bruising,
556 cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,⁷
557 flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and
558 hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy,
559 paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus,
560 pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn
561 susceptibility increased, sweating, urticaria, vasculitis (including Wegener's
562 granulomatosis; see **PRECAUTIONS:** *Hypersensitivity*), abnormal wound healing
563 (delayed healing or exuberant granulation tissue with crusting; see **PRECAUTIONS:**
564 *Information for Patients and Prescribers*)
- 565 *Special Senses: Hearing:* hearing impairment (see **WARNINGS:** *Hearing Impairment*),
566 tinnitus. *Vision:* corneal opacities (see **WARNINGS:** *Corneal Opacities*), decreased
567 night vision which may persist (see **WARNINGS:** *Decreased Night Vision*), cataracts,
568 color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic
569 neuritis, photophobia, visual disturbances
- 570 *Urinary System:* glomerulonephritis (see **PRECAUTIONS:** *Hypersensitivity*), nonspecific
571 urogenital findings (see **PRECAUTIONS:** *Laboratory* for other urological parameters)
- 572 **Laboratory:** Elevation of plasma triglycerides (see **WARNINGS:** *Lipids*), decrease in
573 serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during
574 treatment
- 575 Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see
576 **WARNINGS:** *Hepatotoxicity*)
- 577 Elevation of fasting blood sugar, elevations of CPK (see **PRECAUTIONS:** *Laboratory*
578 *Tests*), hyperuricemia
- 579 Decreases in red blood cell parameters, decreases in white blood cell counts (including
580 severe neutropenia and rare reports of agranulocytosis; see **PRECAUTIONS:** *Information*
581 *for Patients and Prescribers*), elevated sedimentation rates, elevated platelet counts,
582 thrombocytopenia

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

584 **OVERDOSAGE:** The oral LD₅₀ of isotretinoin is greater than 4000 mg/kg in rats and
585 mice (>300 times the maximum clinical dose after normalization of the rat dose for total
586 body surface area and >150 times the maximum clinical dose after normalization of the
587 mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (327
588 times the maximum clinical dose after normalization for total body surface area). In
589 humans, overdosage has been associated with vomiting, facial flushing, cheilosis,
590 abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without
591 apparent residual effects.

592 **DOSAGE AND ADMINISTRATION:** The recommended dosage range for Accutane is
593 0.5 to 2 mg/kg given in 2 divided doses daily for 15 to 20 weeks. In studies comparing
594 0.1, 0.5, and 1 mg/kg/day,⁸ it was found that all dosages provided initial clearing of
595 disease, but there was a greater need for retreatment with the lower dosages.

596 It is recommended that for most patients the initial dosage of Accutane be 0.5 to 1
597 mg/kg/day. Patients whose disease is very severe or is primarily manifested on the trunk
598 may require up to the maximum recommended dosage, 2 mg/kg/day. During treatment,
599 the dose may be adjusted according to response of the disease and/or the appearance of
600 clinical side effects — some of which may be dose related.

601 If the total nodule count has been reduced by more than 70% prior to completing 15 to 20
602 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off
603 therapy, and if warranted by persistent or recurring severe nodular acne, a second course
604 of therapy may be initiated. The optimal interval before retreatment has not been defined
605 for patients who have not completed skeletal growth (see WARNINGS: *Skeletal:*
606 *Hyperostosis and Premature Epiphyseal Closure*).

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

609 Accutane should be administered with food.

ACUTANE DOSING BY BODY WEIGHT

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

610

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611 **Information for Pharmacists:** Accutane must only be dispensed in no more than a
612 1-month supply and only on presentation of an Accutane prescription with a yellow self-
613 adhesive Accutane Qualification Sticker written within the previous 7 days. **REFILLS**
614 **REQUIRE A NEW WRITTEN PRESCRIPTION WITH AN ACCUTANE**
615 **QUALIFICATION STICKER WITHIN THE PREVIOUS 7 DAYS.** No telephone or
616 computerized prescriptions are permitted.

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

620 **HOW SUPPLIED:** Soft gelatin capsules, 10 mg (light pink), imprinted ACCUTANE 10
621 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0155-
622 49).

623 Soft gelatin capsules, 20 mg (maroon), imprinted ACCUTANE 20 ROCHE. Boxes of
624 100 containing 10 Prescription Paks of 10 capsules (NDC 0004-0169-49).

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

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

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644

645

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

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

650
651 Read each item below and initial in the space provided to show that you understand each
652 item and agree to follow your prescriber's instructions. **Do not sign this consent and do**
653 **not take Accutane if there is anything that you do not understand.**

654
655 *A parent or guardian of a minor patient (under age 18) must also read and initial each
656 item before signing the consent.

657
658 _____
659 (Patient's Name)

660
661
662 1. I understand that there is a very high risk that my unborn baby could have severe birth
663 defects if I am pregnant or become pregnant while taking Accutane in any amount
664 even for short periods of time. This is why I must not be pregnant while taking
665 Accutane.

666
667 Initial: _____

668
669 2. I understand that I must not take Accutane (isotretinoin) if I am pregnant.

670
671 Initial: _____

672
673 3. I understand that I must not get pregnant during the entire time of my treatment and
674 for 1 month after the end of my treatment with Accutane.

675
676 Initial: _____

677
678 4. I understand that I must avoid sexual intercourse completely, or I must use 2 separate,
679 effective forms of birth control (contraception) **at the same time**. The only exception
680 is if I have had surgery to remove the womb (a hysterectomy).

681
682 Initial: _____

683

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

689
690 Initial: _____
691

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

696
697 Initial: _____
698

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

700
701 Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills,
702 injectable/implantable/insertable hormonal birth control products, and an
703 IUD (intrauterine device).

704 Secondary: Diaphragms, latex condoms, and cervical caps. Each must
705 be used with a spermicide, which is a special cream or jelly that kills
706 sperm.

707
708 I understand that at least one of my two methods of birth control must be a primary
709 method.

710
711 Initial: _____
712

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

716
717 Initial: _____
718

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

721
722 Initial: _____
723

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

730
731 Initial: _____

732
733 11. I understand that I should not start taking Accutane until I am sure that I am not
734 pregnant and have negative results from 2 pregnancy tests.

735
736 Initial: _____

737
738 12. I have read and understand the materials my prescriber has given to me, including the
739 brochure *Important Information Concerning Your Treatment with Accutane*®
740 (*isotretinoin*). My prescriber gave me and asked me to watch the video about
741 contraception. I was told about a confidential counseling line that I may call for more
742 information about birth control. I have received information on emergency
743 contraception (birth control).

744
745 Initial: _____

746
747 13. I understand that I must stop taking Accutane right away and inform my prescriber if
748 I get pregnant, miss my menstrual period, stop using birth control, or have sexual
749 intercourse without using my two birth control methods at any time.

750
751 Initial: _____

752
753 14. My prescriber gave me information about the confidential Accutane Survey and
754 explained to me how important it is to take part in the Accutane Survey.

755
756 Initial: _____

757
758 15. I understand that the yellow self-adhesive Accutane Qualification Sticker on my
759 prescription for Accutane means that I am qualified to receive an Accutane
760 prescription, because I:

- 761
- 762 • have had two negative urine or serum pregnancy tests before receiving the initial
763 Accutane prescription. I must have a negative result from a urine or serum
764 pregnancy test repeated each month prior to my receiving each subsequent
765 prescription.
 - 766
 - 767 • have selected and committed to use two forms of effective contraception
768 simultaneously, at least one of which must be a primary form, unless absolute
769 abstinence is the chosen method, or I have undergone a hysterectomy. I must use
770 two forms of contraception for at least 1 month prior to initiation of Accutane

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771 therapy, during therapy, and for 1 month after discontinuing therapy. I must
772 receive counseling, repeated on a monthly basis, about contraception and
773 behaviors associated with an increased risk of pregnancy.
774

- 775 • have signed a Patient Information/Consent form that contains warnings about the
776 risk of potential birth defects if I am pregnant or become pregnant and my unborn
777 baby is exposed to isotretinoin.
- 778
- 779 • have been informed of the purpose and importance of participating in the
780 Accutane Survey and given the opportunity to enroll.
- 781

782 ***My prescriber has answered all my questions about Accutane and I understand that it***
783 ***is my responsibility not to get pregnant during Accutane treatment or for a month after***
784 ***I stop taking Accutane.***

785
786 Initial: _____

787
788 I now authorize my prescriber _____ to begin my treatment with Accutane.
789

790 Patient signature: _____ Date: _____

791
792 Parent/guardian signature(if under age 18): _____ Date: _____

793
794 Please print: Patient name and address _____

795
796 _____ Telephone (area code) _____

797
798 I have fully explained to the patient, _____, the nature and purpose of the
799 treatment described above and the risks to females of childbearing potential. I have
800 asked the patient if she has any questions regarding her treatment with Accutane and have
801 answered those questions to the best of my ability.

802
803 Prescriber signature: _____ Date: _____

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819 **INFORMED CONSENT/PATIENT AGREEMENT (for all patients):**

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

822 Read each item below and initial in the space provided if you understand each item and
823 agree to follow your prescriber's instructions. A parent or guardian of a patient under age
824 18 must also read and understand each item before signing the agreement.

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

827

828 1. I, _____,

829

(Patient's Name)

830

831 understand that Accutane is a medicine used to treat severe nodular acne that cannot
832 be cleared up by any other acne treatments, including antibiotics. In severe nodular
833 acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular
834 acne can lead to permanent scars.

834

835 Initials: _____

836

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

838

839 Initials: _____

840

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

845

846 Initials: _____

847

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

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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 than usual
- 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: _____

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

909
910 Initials: _____

911
912 11. I have read the brochure *Important Information Concerning Your Treatment with*
913 *Accutane* and other materials my provider gave me containing important safety
914 information about Accutane. I understand all the information I received.

915
916 Initials: _____

917
918 12. My prescriber and I have decided I should take Accutane. I understand that each of
919 my Accutane prescriptions must have a yellow self-adhesive Accutane Qualification
920 Sticker on it. I understand that I can stop taking Accutane at any time. I agree to tell
921 my prescriber if I stop taking Accutane.

922
923 Initials: _____

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

926
927 Patient Signature: _____ Date:
928 _____

929
930 Parent/Guardian Signature (if under age 18): _____ Date:
931 _____

932
933 Patient Name (print) _____

934
935 Patient Address _____

936 Telephone (____.____.____) _____
937 _____

938 I have:

939

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

947

948 Prescriber Signature: _____

949 Date: _____

950

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951

952 MEDICATION GUIDE:

953

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

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

958

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

965

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

968

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

976

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

979

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

992

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

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996

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

997

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999

What are the important warnings for females taking Accutane?

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1007

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.

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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 five 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.

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

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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.

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

1029

1030

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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.

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1038

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.

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All patients should read the rest of this Medication Guide.

1041

1042

What are the signs of mental problems?

1043

1044

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.

1045

1046

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.

1047

1048

1049

1050

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

1051

1052

- Start to feel sad or have crying spells

1053

- Lose interest in activities you once enjoyed

1054

- Sleep too much or have trouble sleeping

1055

- Become more irritable than usual

1056

- Have a change in your appetite or body weight

1057

- Have trouble concentrating

1058

- Withdraw from your friends or family

1059

- Feel like you have no energy

1060

- Have feelings of worthlessness or inappropriate guilt

1061

- Start having thoughts about hurting yourself or taking your own life (suicidal thoughts)

1062

1063

1064

1065

What is Accutane?

1066

1067

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.

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Who should not take Accutane?

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1077

- **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.

1078

1079

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1081

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- 1082 • Do not take Accutane unless you completely understand its possible risks and are
1083 willing to follow all of the instructions in this Medication Guide.

1084

1085 Tell your prescriber if you or someone in your family has had any kind of mental
1086 problems, asthma, liver disease, diabetes, heart disease, or any other important health
1087 problems. Tell your prescriber about any food or drug allergies you have had in the past.
1088 These problems do not necessarily mean you cannot take Accutane, but your prescriber
1089 needs this information to discuss if Accutane is right for you.

1090

1091 How should I take Accutane?

1092

- 1093 • You will get no more than a 1 month supply of Accutane at a time, to be sure you
1094 check in with your prescriber each month to discuss side effects.
- 1095 • Your prescription should have a special yellow self-adhesive sticker attached to it.
1096 The sticker is YELLOW. If your prescription does not have this yellow self-adhesive
1097 sticker, call your prescriber. The pharmacy should not fill your prescription unless it
1098 has the yellow self-adhesive sticker.
- 1099 • The amount of Accutane you take has been specially chosen for you and may change
1100 during treatment.
- 1101 • You will take Accutane 2 times a day with food, unless your prescriber tells you
1102 otherwise.
- 1103 • If you miss a dose, just skip that dose. Do **not** take 2 doses the next time.
- 1104 • You should return to your prescriber as directed to make sure you don't have signs of
1105 serious side effects. Because some of Accutane's serious side effects show up in
1106 blood tests, some of these visits may involve blood tests (monthly visits for female
1107 patients should always include a urine or serum pregnancy test).

1108

1109 What should I avoid while taking Accutane?

1110

- 1111 • **Do not get pregnant** while taking Accutane. See "What is the most important
1112 information I should know about Accutane?" and "What are the important warnings
1113 for females taking Accutane?"
- 1114 • **Do not breast feed** while taking Accutane and for 1 month after stopping Accutane.
1115 We do not know if Accutane can pass through your milk and harm the baby.
- 1116 • **Do not give blood** while you take Accutane and for 1 month after stopping Accutane.
1117 If someone who is pregnant gets your donated blood, her baby may be exposed to
1118 Accutane and may be born with birth defects.
- 1119 • **Do not take Vitamin A** supplements. Vitamin A in high doses has many of the same
1120 side effects as Accutane. Taking both together may increase your chance of getting
1121 side effects.
- 1122 • **Do not have cosmetic procedures to smooth your skin, including waxing,
1123 dermabrasion, or laser procedures, while you are using Accutane and for at least
1124 6 months after you stop.** Accutane can increase your chance of scarring from these

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1125 procedures. Check with your prescriber for advice about when you can have cosmetic
1126 procedures.

- 1127 • **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use
1128 ultraviolet lights. Accutane may make your skin more sensitive to light.
- 1129 • **Do not use birth control pills that do not contain estrogen (“minipills”).** They
1130 may not work while you take Accutane. Ask your prescriber or pharmacist if you are
1131 not sure what type you are using.
- 1132 • **Talk with your doctor if you plan to take other drugs or herbal products.** This is
1133 especially important for patients using birth control pills and other hormonal types of
1134 birth control because the birth control may not work as effectively if you are taking
1135 certain drugs or herbal products. You should not take the herbal supplement, St.
1136 John’s Wort because this herbal supplement may make birth control pills not work as
1137 effectively.
- 1138 • **Do not share Accutane with other people.** It can cause birth defects and other
1139 serious health problems.
- 1140 • **Do not take Accutane with antibiotics unless you talk to your prescriber.** For
1141 some antibiotics, you may have to stop taking Accutane until the antibiotic treatment
1142 is finished. Use of both drugs together can increase the chances of getting increased
1143 pressure in the brain.

1144

1145 **What are the possible side effects of Accutane?**

1146

1147 **Accutane has possible serious side effects**

1148

- 1149 • **Accutane can cause birth defects, premature births, and death in babies** whose
1150 mothers took Accutane while they were pregnant. See “What is the most important
1151 information I should know about Accutane?” and “What are the important warnings
1152 for females taking Accutane?”
- 1153
- 1154 • **Serious mental health problems.** See “What is the most important information I
1155 should know about Accutane?”
- 1156
- 1157 • **Serious brain problems.** Accutane can increase the pressure in your brain. This can
1158 lead to permanent loss of sight, or in rare cases, death. Stop taking Accutane and call
1159 your prescriber right away if you get any of these signs of increased brain pressure:
1160 bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients
1161 taking Accutane have had seizures (convulsions) or stroke.
- 1162
- 1163 • **Abdomen (stomach area) problems.** Certain symptoms may mean that your internal
1164 organs are being damaged. These organs include the liver, pancreas, and bowel
1165 (intestines). If your organs are damaged, they may not get better even after you stop
1166 taking Accutane. Stop taking Accutane and call your prescriber if you get severe
1167 stomach or bowel pain, diarrhea, rectal bleeding, yellowing of your skin or eyes, or
1168 dark urine.

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1170 • **Bone and muscle problems.** Accutane may affect bones, muscles, and ligaments and
1171 cause pain in your joints or muscles. Tell your prescriber if you plan vigorous
1172 physical activity during treatment with Accutane. Tell your prescriber if you develop
1173 pain. If a bone breaks, tell your prescriber you take Accutane. No one knows if taking
1174 Accutane for acne will reduce bone healing or stunt growth.

1175

1176 • **Hearing problems.** Some people taking Accutane have developed hearing problems.
1177 It is possible that hearing loss can be permanent. Stop using Accutane and call your
1178 prescriber if your hearing gets worse or if you have ringing in your ears.

1179

1180 • **Vision problems.** While taking Accutane you may develop a sudden inability to see
1181 in the dark, so driving at night can be dangerous. This condition usually clears up
1182 after you stop taking Accutane, but it may be permanent. Other serious eye effects
1183 can occur. Stop taking Accutane and call your prescriber right away if you have any
1184 problems with your vision or dryness of the eyes that is painful or constant.

1185

1186 • **Lipid (fats and cholesterol in blood) problems.** Many people taking Accutane
1187 develop high levels of cholesterol and other fats in their blood. This can be a serious
1188 problem. Return to your prescriber for blood tests to check your lipids and to get any
1189 needed treatment. These problems generally go away when Accutane treatment is
1190 finished.

1191

1192 • **Allergic reactions.** In some people, Accutane can cause serious allergic reactions.
1193 Stop taking Accutane and get emergency care right away if you develop hives, a
1194 swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your
1195 prescriber if you develop a fever, rash, or red patches or bruises on your legs.

1196

1197 • **Signs of other possibly serious problems.** Accutane may cause other problems. Tell
1198 your prescriber if you have trouble breathing (shortness of breath), are fainting, are
1199 very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech,
1200 problems moving, or any other serious or unusual problems. Frequent urination and
1201 thirst can be signs of blood sugar problems.

1202

1203 Serious permanent problems do not happen often. However, because the symptoms listed
1204 above may be signs of serious problems, if you get these symptoms, stop taking Accutane
1205 and call your prescriber. If not treated, they could lead to serious health problems. Even if
1206 these problems are treated, they may not clear up after you stop taking Accutane.

1207 Accutane has less serious possible side effects

1208 The common less serious side effects of Accutane are dry skin, chapped lips, dry eyes,
1209 and dry nose that may lead to nosebleeds. People who wear contact lenses may have
1210 trouble wearing them while taking Accutane and after therapy. Sometimes, people's acne

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1211 may get worse for a while. They should continue taking Accutane unless told to stop by
1212 their prescriber.

1213 These are not all of Accutane's possible side effects. Your prescriber or pharmacist can
1214 give you more detailed information that is written for health care professionals.

1215 This Medication Guide is only a summary of some important information about
1216 Accutane. Medicines are sometimes prescribed for purposes other than those listed in a
1217 Medication Guide. If you have any concerns or questions about Accutane, ask your
1218 prescriber. Do not use Accutane for a condition for which it was not prescribed.

1219 **Active Ingredient: Isotretinoin.**

1220 Inactive Ingredients: beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated
1221 soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain
1222 glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg —
1223 iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1,
1224 and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium
1225 dioxide.

1226
1227 This Medication Guide has been approved by the U.S. Food and Drug Administration.
1228
1229

1230 R_x only



Pharmaceuticals

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Nutley, New Jersey 07110-1199

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(Cover)

Accutane® (isotretinoin)

System to Manage Accutane Related Teratogenicity™

S.M.A.R.T.™ Guide to Best Practices

((PPP logo))

((ROCHE Pharmaceuticals))

Page 2

Accutane® (isotretinoin) is indicated for the treatment of severe recalcitrant nodular acne. In addition, for female patients of childbearing potential, Accutane is indicated only for those females who are not pregnant (see boxed CONTRAINDICATIONS AND WARNINGS).

Guidelines for Successful Outcomes

Important Facts About Accutane

- Accutane is highly teratogenic.
- Treatment with Accutane during pregnancy is contraindicated. Female patients should not be pregnant or become pregnant while on Accutane therapy and for 1 month thereafter.
- Fetal exposure to isotretinoin may result in life threatening congenital abnormalities.

The S.M.A.R.T. *Guide to Best Practices*

This guide has been developed to assist you in fulfilling the requirements for Accutane pregnancy prevention risk management, the Accutane boxed CONTRAINDICATIONS and WARNINGS and the Precautions of the Accutane Product Information.

The following is the Black Box Warning from the approved labeling for Accutane:

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 micropthalmia), 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 a month after stopping Accutane. To help patients have the knowledge and tools to do so, 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 before beginning treatment of female patients with Accutane
 - 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 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 Stickers signifies that she:

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial 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 five 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. The manufacturer will make available urine pregnancy test kits for female Accutane patients for the initial, second and monthly testing during therapy.
- Must have selected and has committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a

hysterectomy. Patients must use two forms of effective contraception for at least one month prior to initiation of Accutane therapy, during Accutane therapy, and for one 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 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 two 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

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

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

The yellow self-adhesive Accutane Qualification Sticker documents that the female patient was 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: check off the "male" gender box without checking the qualification statement.

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 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 1-MONTH SUPPLY**
- **ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **WRITTEN WITHIN THE PREVIOUS 7 DAYS**
- **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.

Please see the enclosed complete product information, including boxed CONTRAINDICATIONS AND WARNINGS, in pocket.

((ROCHE diamond logo))

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About Accutane¹

Accutane is a powerful agent used to treat severe recalcitrant nodular acne. Accutane belongs to a class of drugs known as retinoids, commonly understood to include all natural and synthetic analogues of vitamin A. Therapy with Accutane should not be undertaken before conventional treatment has been tried first, including the use of systemic antibiotic therapy, and the patient has been fully counseled about the warnings and precautions in the Accutane package insert.

Accutane is teratogenic and must not be used by pregnant women. Women should not become pregnant within 1 month after discontinuing Accutane therapy. A patient who becomes pregnant during treatment should stop taking Accutane and immediately contact her prescriber.

Accutane use is associated with other potentially serious adverse events, as well as more frequent, but less serious side effects. More frequent, less serious side effects include cheilitis, dry skin, skin fragility, pruritus, epistaxis, dry nose and dry mouth, and conjunctivitis.

Adverse Event Warnings include psychiatric disorders*: (depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide); pseudotumor cerebri; pancreatitis; hyperlipidemia; hearing impairment*; hepatotoxicity; inflammatory bowel disease; skeletal changes: (hyperostosis, premature epiphyseal closure;); visual impairment: (corneal opacities, decreased night vision).

*No mechanism of action has been established for these events.

Patients should be reminded to read the Medication Guide, distributed by the pharmacist at the time the Accutane is dispensed.

Pregnancy after Accutane therapy

The terminal elimination half-life of Accutane varies but is generally within 10 to 20 hours. The elimination half-life of one of the isotretinoin metabolites, 4-oxoisotretinoin is approximately 25 hours. Since plasma elimination is host dependent, prescribers should warn patients not to become pregnant for 1 month post treatment. Women who become pregnant during this month should be counseled as to the outcome data. In 1989, Dai et al² reported the results of an epidemiologic study of pregnancies that occurred in women who conceived after discontinuing Accutane. They studied women ≤ 5 - greater than 60 days between their last dose of isotretinoin and conception. The incidence of birth defects in former Accutane patients was not significantly different from the rate in the general population.

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 post-marketing 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.

Birth Defects

There is an extremely high risk that a deformed infant will result if pregnancy occurs while female patients are taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. Not every fetus exposed to Accutane has resulted in a deformed child; however, there are no accurate means of determining which fetus has been affected and which fetus has not been affected.

When Accutane is taken during pregnancy, it has been associated with fetal malformations, and there is an increased risk for spontaneous abortions, and premature birth.

The following human fetal abnormalities have been documented:

External abnormalities

Skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia), facial dysmorphia; cleft palate.

((EXTERNAL ABNORMALITIES PICTURE GOES HERE))

((COPY UNDER DRAWING))

Line drawing represents the possible abnormalities of lowset deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.

Internal abnormalities

CNS abnormalities including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit; cardiovascular abnormalities; thymus gland abnormalities; parathyroid hormone deficiencies.

In some cases death has occurred with certain of the abnormalities noted.

((LINE DRAWING OF INTERNAL ABNORMALITIES GOES HERE))

((COPY UNDER DRAWING))

Line drawing represents the possible abnormalities of the brain, heart, and thymus gland that may occur.

Accutane Pregnancy Prevention Risk Management

The Accutane pregnancy prevention risk management program consists 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. The components of S.M.A.R.T. are:

- 1) The booklet entitled System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Guide to Best Practices
- 2) A S.M.A.R.T. *Letter of Understanding* containing the Prescriber Checklist
- 3) A yellow self-adhesive Accutane Qualification Sticker to be affixed to your prescription form.

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* and understand their responsibilities to minimize the risk of fetal exposure to Accutane, and understand how to qualify female patients for an Accutane prescription (see boxed CONTRAINDICATIONS AND WARNINGS).

The Prescriber Checklist is a self-certification by potential Accutane prescribers:

- 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 a month after stopping Accutane. To help patients have the knowledge and tools to do so, 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 before beginning treatment of female patients with Accutane
- 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 Accutane Qualification Stickers

- 3) The yellow self-adhesive Accutane® Qualification Sticker is documentation for the dispensing pharmacist that the prescriber has qualified the female patient according to the qualification criteria in the boxed CONTRAINDICATIONS AND WARNINGS of the approved package insert.

Prescribers must obtain yellow self-adhesive Accutane Qualification Stickers designed to adhere to the center portion of the patient's Accutane prescription (see sticker diagram below). The yellow self-adhesive Accutane Qualification Stickers can only be obtained by reading the S.M.A.R.T. *Guide to Best Practices* and signing and returning the completed S.M.A.R.T. *Letter of Understanding*. Additional Accutane Qualification Stickers can then be obtained by calling 1-800-93-ROCHE toll-free.

((INSERT STICKER DIAGRAM HERE))

Pharmacists will have the option to verify the authorization for the yellow self-adhesive Accutane Qualification Sticker by calling 1-800-93-ROCHE, but this step is not required. Accutane prescriptions should not be filled more than 7 days after patient qualification.

The yellow self-adhesive Accutane Qualification Sticker should also be used on prescriptions for **male patients** (check "male gender" box and do not fill out qualification date). Thus, *ALL prescriptions for Accutane should have the special yellow sticker.*

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Qualifying Female Patients

Data support that there are key issues in identifying female patients for treatment with Accutane: 1) identify patients whose acne could be effectively managed without Accutane and avoid prescribing it for such patients; 2) identify those who are already pregnant when you are considering Accutane; and 3) identify those who may not be reliable in avoiding pregnancy for the required period before, during and after therapy.

The patient should understand that ultimately, it is her responsibility to avoid exposing an unborn baby to Accutane. The patient must understand the critical responsibility she assumes in electing to undertake therapy with Accutane and that any method of birth control, apart from complete abstinence, can fail.

The prescriber must verify that each individual patient receives adequate counseling about all her pregnancy prevention options (including abstinence) and that she knows how to select and use two separate, effective contraceptive methods.

The Qualification Criteria for female patients are:

- **Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second**

pregnancy test (a confirmation test) should be done during the first five 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. The manufacturer will make available urine pregnancy test kits for female Accutane patients for the initial, second and monthly testing during therapy.

- **Must have selected and committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of effective contraception for at least one month prior to initiation of Accutane therapy, during Accutane therapy, and for one 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 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 two 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

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

reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

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

((Side Bars))

Reports indicate that 14% of the women who reported being pregnant during Accutane therapy were pregnant at the time Accutane was initially prescribed and either did not have a pregnancy test or did not wait for the results of the pregnancy test. Be sure to establish negative pregnancy status at the time of the screening visit and BEFORE giving the patient a prescription for Accutane.

Reports indicate that 12% of the women who reported being pregnant during Accutane therapy became pregnant after obtaining and beginning Accutane therapy, but before their next menses. Be sure to confirm negative pregnancy status during the first 5 days of the normal menses immediately preceding the start of Accutane therapy (some contraception methods, for example hormone implants, may cause amenorrhea. In that case, the second test should be done at least 11 days after the last act of unprotected sexual intercourse [without using 2 separate effective forms of contraception]).

Reports indicate that 64% of the women who reported being pregnant during therapy had not been able to avoid behavior that created a high risk of pregnancy. Pregnancy occurred most often when only using one form of birth control. Continued monthly counseling is critical to maintaining negative pregnancy status. Continued negative pregnancy status must be confirmed by monthly pregnancy testing. Hysterectomy and reliable abstinence are the only exceptions to the use of dual contraceptive methods. However, ALL female patients MUST undergo monthly pregnancy testing in order to receive Accutane.

Please read this Guide carefully and use the Pregnancy Prevention Program with EVERY female patient.

Please see the enclosed complete product information, including boxed CONTRAINDICATIONS AND WARNINGS, in pocket.

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(S.M.A.R.T.)Procedures

S.M.A.R.T. is described fully within the boxed CONTRAINDICATIONS and WARNINGS and the Precautions sections of the Accutane package insert. The following

provides the necessary steps prescribers must take to be in compliance with the risk management components of the Accutane package insert.

➤ **To receive the first shipment of Qualification Stickers :**

1. Read the *S.M.A.R.T.™ Guide to Best Practices* (enclosed)
2. Sign and return, in the postage paid envelope provided, the completed *S.M.A.R.T. Letter of Understanding™*(enclosed), which states:
 - 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 a month after stopping Accutane. To help patients have the knowledge and tools to do so, 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 before beginning treatment of female patients with Accutane
 - 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 Accutane Qualification Stickers

Additional Stickers can then be obtained as needed by calling 1-800-93-ROCHE

Prior to writing the Accutane prescription:

Obtain screening and confirmation pregnancy tests for ALL female patients. Ensure each female patient is *qualified* according to criteria identified in the Boxed Warning of the package insert.

Monthly visits:

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

Roche supports an initial referral to a contraception counselor trained to provide family planning services for contraceptive counseling should you feel that this is necessary. A

referral form is contained within the booklet, *Be Smart, Be Safe, Be Sure™ Accutane® Pregnancy Prevention and Risk Management Program for Women*.

S.M.A.R.T. Outcomes

To measure the progress of S.M.A.R.T., Roche will use several outcomes approaches.

Roche will continue to track how many women join the Accutane Survey, which is conducted by the Slone Epidemiology Unit of the Boston University School of Public Health. Roche has committed to increasing enrollment of female patients to 60% from 25-40% currently. We understand that this number will be difficult to accomplish, and we therefore ask prescribers to remind and encourage patients to join the Accutane Survey. An application form is contained inside both the female patient booklet, *Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women* and in the Accutane blister pak.

Further, an independent audit of pharmacies will be performed to assess the use of the Accutane Qualification Stickers. As part of the validation for this component, the audit will be both retrospective and prospective in nature. The data collected will not be identifiable to any specific prescriber or patient.

Page 8 & 9 with thumbnails

The Accutane Pregnancy Prevention Program

The Accutane Pregnancy Prevention Program is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The PPP consists of information on the risks and benefits of Accutane, which is linked to the Accutane Medication Guide.

Information for male and female patients is provided in separate booklets, called *Be Smart, Be Safe, Be Sure™ Accutane® Pregnancy Prevention and Risk Management Program for Women* and *Be Smart, Be Safe, Be Sure™ Accutane® Risk Management Program for Men*. Each booklet contains information on Accutane therapy, including precautions and warnings, an Informed Consent/Patient Agreement form, and a toll-free line that provides Accutane information in 13 languages.

How to use the Pregnancy Prevention Program® for Women on Accutane® (isotretinoin)

Educating Female Patients

Patient Product Information: Important Information Concerning Your Treatment with Accutane® (isotretinoin)

Patient education material for Accutane that provides complete pregnancy warnings to female patients, plus information about severe recalcitrant nodular acne and what to

expect with treatment, including warnings and precautions. The patient may refer to this information throughout therapy.

Contraception Counseling Referral Program

Your patient may benefit from FREE expert contraception counseling; Roche will reimburse consultant specialists who provide this service. Details covering reimbursement criteria are available on the form itself or by calling Roche.

Obtaining Consent

Accutane Survey Enrollment Form

An enrollment form for the Accutane Survey, a confidential survey independently by Slone Epidemiology Unit of the Boston University School of Public Health. Please encourage your female patients to enroll while they are completing the rest of the forms. And please keep reminding them monthly until they do.

Informed Consent/Patient Agreement for All Patients

A form that helps to document that the patient and/or her parent/guardian* understand the risks of treatment with Accutane, including potential adverse events. The form's comprehensive list of points makes it an important addition to her file.

*If patient is a minor under the age of 18.

Patient Information/Consent for Female Patients

A form that helps document that the patient and/or her parent/guardian* understand the teratogenic risks of treatment with Accutane, the need to avoid pregnancy, and her responsibilities before, during and after therapy. The form's comprehensive list of points makes it an important addition to her file.

*If patient is a minor under the age of 18.

Patient Qualification Form

A form that confirms that a female patient has met the four qualification criteria as outlined in the boxed CONTRAINDICATIONS and WARNINGS in the Accutane package insert.

Reinforcing Education

Preventing Pregnancy—A Guide to Contraception

Information your patient needs to know about the optimal use of various contraception methods, especially those that are considered primary and secondary methods and the myths that influence the behavioral factors in pregnancy risk.

Contraception Knowledge Test

A tool that helps the prescriber assess each female patient's level of compliance and knowledge of contraception. This 10-question test is located at the back of the guide, *Preventing Pregnancy—A Guide to Contraception*, and should be completed by the patient after reading that guide.

Accutane® InfoLine

Useful for every female patient, but especially those who have difficulty reading, the Accutane InfoLine is a toll-free telephone service that provides an audio version of the pregnancy warnings. The Accutane InfoLine supports English, Spanish and the 11 other most widely spoken languages - 13 in all. The Accutane InfoLine toll-free number is 1-800-950-4411.

Confidential Contraception Counseling Line

The Confidential Contraception Counseling Line is a 24-hour toll-free telephone line that provides patient information on Accutane, pregnancy, contraception and pregnancy prevention. As always, patients are referred to their prescriber for additional information and clarification. The Confidential Contraception Counseling Line toll-free number is 1-800-542-6900.

Be Prepared, Be Protected Video/Storyboard

This nonbranded video provides no-nonsense information about contraception and the risk of pregnancy for female patients. It is available for you to give to female patients.

Additional components of the Accutane® Pregnancy Prevention Program® for Prescribers

Additional components of the Accutane® Pregnancy Prevention Program® have been developed to help in achieving success. To receive these components, please request them by calling 1-800-93-ROCHE.

Free urine pregnancy test kits

The kits contain the same tests that are validated and used by clinical laboratories and are sensitive at 25 mIU/mL (after about 7 days after conception). The tests are 99% accurate only 11 days after conception. Please refer to the expiration date stamped on individual boxes and pouches, and observe storage requirements. The kits come with a dispenser box and tear-off instruction sheets, in both English and Spanish. The ASI urine test kits currently being supplied are waived under the CLIA regulations, because the results are observed as a colored band, which requires only simple interpretation.

Accutane® Continuation/Progress Notes pads

Pads of 50 Accutane Continuation/Progress Notes are available. Each sheet has important reminders for everyone on your staff who interacts with female Accutane patients. There is a printed checklist for every visit, with a series of questions about sexual activity and methods of contraception used since the last visit.

Please see the enclosed complete product information, including boxed CONTRAINDICATIONS AND WARNINGS, in pocket.

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Meeting the 4 Female Qualification Criteria

1. **Female patients must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first five 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.**

Pregnancy Testing

Human chorionic gonadotropin (hCG) is a glycoprotein hormone normally produced during pregnancy from the chorion, which is the membrane that becomes a placenta. In a normal pregnancy, hCG can be detected in serum and urine about 7 days following conception.

Levels of hCG double every 2 days for the first 3-4 weeks following implantation of the embryo.

	Days	hCG levels (mIU/mL)
Men		0
Nonpregnant women		0
Pregnant women	7-10 days after conception	10-30
	12-16 days after conception	50-250
	42-112 days after conception	37,000-50,000
	Peak	50,000
	Remainder of the pregnancy	Decreases by 10%-30%
Postpartum women	14 days postpartum	50
	12-16 days postpartum	0

Pregnancy testing can be done either by using serum or urine. Both serum and urine testing report a level of hCG.

The ASI Urine Pregnancy Tests

The ASI urine pregnancy tests are a system combining monoclonal and polyclonal antibodies, which will detect hCG with a high degree of specificity and sensitivity. This detection is possible 10-14 days post conception.

The ASI ProPhase Plus™ cassette, provided by Roche, is an immunochromatographic monoclonal and polyclonal antibodies system containing a unique set of dye-conjugated and immobilized antibodies, which produce a distinctive visual pattern in the results window when the hCG concentration is greater than 25 mIU/mL.

The urine sample migrates through the absorbent area, mixing with labeled antibody-dye conjugate; hCG present in the specimen binds to the conjugate, forming an antibody-antigen complex. As the reaction mixture flows through the test zone “T,” the complex binds to immobilized anti-hCG, producing a pink rose color band. The appearance of the color band in the test zone indicates that hCG is present at or above the lowest cutoff sensitivity of 25 mIU/mL. In the control zone “C,” unbound conjugate binds to immobilized reagents producing a pink rose band. The appearance of this band indicates that the test is functioning properly.

The sensitivity is standardized against the World Health Organization International Reference Preparation (WHO 1st IRP). Data from clinical testing by the manufacturer indicate that when directions are followed, barring human error, the tests are 99% accurate.

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Assessing Reproductive Health and Contraception Methods Before Prescribing Accutane

2. The female patient must have selected and committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of contraception for at least 1 month prior to initiation of Accutane therapy, during 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.

For the last 20 years, convenient once-a-day oral contraceptives have been available, and therefore procreation decisions can be made through conscious choice; and yet every year half of the pregnancies in the US are unintended or mistimed. Data support that 64% of the reported pregnancies with Accutane occurred in women who became pregnant after beginning Accutane therapy. There are many reasons why unplanned pregnancies occur. The most common reasons for these pregnancies are:

- Inability to maintain absolute abstinence
- Use of ineffective contraceptive methods
- Inconsistent use of effective contraception
- Unexpected sexual intercourse
- Contraceptive method failure

Better education and the ability to follow instructions precisely can make a difference. Therefore, it is especially important to be able to assess your patient's ability to understand her responsibilities and your instructions, and to reinforce these instructions at every clinical visit.

It is very important to be able to make a careful assessment of a woman's reproductive history, contraceptive knowledge and previous use of contraception methods. This assessment and contraceptive education should continue throughout Accutane treatment. In order to assist in this monthly review, the Accutane Continuation/Progress Notes includes a monthly sexual activity assessment section and checklist on contraception use.

When trying to obtain information, it is important to be aware that the patient may respond to questions according to what she thinks her sexual activity should be, or what she thinks you want to hear, in contrast to what the reality is for her. Because of this, the skill of being able to assess your patient and respond with treatment and counseling specific to her is key to the success of your communication.

- Pay particular attention to nonverbal clues that may lead you to question what was said.
- Some of the overt behaviors to look for are a change in demeanor, a change in eye contact, looking down and uneasiness apparent in body movements.

Interviewing Patients

During the assessment phase:

- Do not allow patients to dismiss questions.

Whether or not a formal tool is used, it is vital that you are sure that the patient understands the questions fully. Pregnancy has occurred in patients who said that they were not sexually active, were using birth control or had an infertile partner.

- Do not assume that an adolescent is not involved in sexual activity.

The percentage of teenage girls having sexual intercourse at earlier ages is gradually rising. About 14% of girls born in the early 1970s had had sexual intercourse by the age of 15¹. Many females seek contraceptive care for the first time as early as mid-adolescence. An adolescent or young adult will be reluctant to discuss her sexuality in front of her parent. If you cannot see her alone, or obtain information from her, perhaps some general questions about relationships and boyfriends will give you an idea of potential risk.

REGARDLESS OF AGE, SOCIO-ECONOMIC STATUS, OR EDUCATION, ALL FEMALES OF CHILD-BEARING POTENTIAL MUST HAVE CONTRACEPTION COUNSELING EITHER BY YOU, YOUR STAFF OR THROUGH USE OF THE CONTRACEPTION COUNSELING REFERRAL PROGRAM.

Please see the enclosed complete product information, including boxed CONTRAINDICATIONS AND WARNINGS, in pocket.

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Confidential Contraception Counseling Line

For those patients who may have questions that they have not asked during the prescriber visits, Roche has provided a Confidential Contraception Counseling Line for patients to obtain contraception information 24 hours a day, 7 days a week. The patient can call a toll-free number (1-800-542-6900) and obtain information on a variety of subjects.

The categories include:

1. Birth defects/teratogenicity
2. Sex and birth control
3. Methods of birth control
4. Emergency contraception
5. Pregnancy and pregnancy testing
6. The Accutane Survey
7. Repeat choices

As always, patients are referred to their prescribers for additional information and clarification.

Educating Patients

Your ability to effectively communicate necessary information to the patient plays a significant role in the degree of compliance achieved. The results from compliance studies consistently focus on the prescriber-patient relationship and the aspects of those relationships that are either productive or counterproductive to patient compliance.³

You must allow sufficient time to provide adequate patient education on contraception. Study results show:

- 50% of patients forget instructional statements immediately after an office visit⁴
- 35% to 92% of patients will not understand general information given to them⁴
- Prescribers overestimated, by a factor of nine, the amount of time they thought they spent on patient education⁵
- In 65% of the cases, prescribers thought that patients wanted less information than they actually did⁵

Encouraging Patient Compliance

Things to do every month of Accutane treatment:

- Repeat pregnancy testing.

Pregnancy testing should be done monthly before each prescription is written during Accutane treatment.

- Prescribe no more than a 1-month supply of Accutane as provided in the package information with a self-adhesive Accutane Qualification Sticker. *Accutane should be prescribed on a monthly basis; no refills, telephone or computerized prescriptions are allowed.*
- Repeat contraception counseling.
Contraception counseling should be repeated on a monthly basis during Accutane treatment so that the patient's concerns and questions are answered in an ongoing basis.

Prescriber-patient interaction that encourages the patient to talk about sensitive sexual issues in an atmosphere that is characterized by interest and friendliness and the absence of prescriber domination results in greater patient satisfaction.⁶ Practice the “four E’s”:

- Engage the patient
- Empathize with the patient
- Educate the patient
- Enlist the patient in her own healthcare

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Contraception During Accutane Therapy

Once you have determined that the patient will require contraception during therapy, you must be thorough in assessing contraception history, explaining the contraception requirements and ensuring that she is educated in contraception methods. Explain to the patient that she must consistently use two separate, effective forms of contraception simultaneously:

- At least 1 month before initiation of Accutane therapy;
- Consistently during Accutane therapy; and
- For 1 month after Accutane therapy stops.

Use the Reinforcement Section of the patient book, *Preventing Pregnancy—A Guide to Contraception*, to help you as you explain the contraception requirements with Accutane treatment.

Assess and address all potential compliance problems with the patient. Ask the patient to tell you what she thinks may cause a compliance problem during her Accutane treatment.

Additionally, it is very important to discuss alcohol and/or drug use with the patient. These substances can impair judgment, lower inhibitions and affect awareness in the patient or her sexual partner, and can significantly impact compliance with contraceptive measures.

Assessing Patient Misinformation About Contraception

Misinformation about contraception can exist regardless of patient age, social status, sexual experience or education. Numerous myths exist regarding conception and how it can be prevented. For example, some mistakenly believe that conception is impossible the first time a person has sexual intercourse. Additionally, some think that douching or having sexual intercourse in a certain position will prevent pregnancy. Additional myths and facts can be found in the patient book, *Preventing Pregnancy—A Guide to Contraception*. However, because it is not possible to identify all existing contraception misinformation that any one patient may have, emphasize to the patient that only specific methods of contraception are recommended while taking Accutane.

Remind your patient that it is imperative to always follow instructions exactly. No matter what two forms of contraception she is using simultaneously, if she uses them inconsistently or incorrectly, she can become pregnant.

Although certain times of a woman's monthly cycle are safer than others, no time exists that is completely safe, which includes during the menses. Many individuals are unaware that conception is possible during this time; this fact should be discussed with your patient.

Remember, not all vaginal bleeding occurs during the hormonal menses. Bleeding can occur off-cycle, or can be a sign of uterine or vaginal infection.

Accessing Contraception Information

Your patient may need assistance accessing affordable contraception counseling. Roche Laboratories Inc., the manufacturer of Accutane, will reimburse a licensed contraception counselor for contraception counseling. Forms to be used for referring your patient to a contraception counselor are part of the individual female patient booklets. Consider establishing a relationship with a reproductive practice(s); in this way, contraception counselors at that practice(s) will be knowledgeable about the contraceptive requirements while taking Accutane.

Discussing the Role of the Sexual Partner

Discuss the patient's sexual partner's involvement in contraception. Encourage the patient to discuss her Accutane treatment and the requirement for continual use of two separate, effective forms of contraception simultaneously, with her sexual partner. Explain and discuss the contents of the section entitled Your Sexual Partner in the Educational Reinforcement Section, *Preventing Pregnancy—A Guide to Contraception*. Encourage her to give the patient guidebook to her partner and to discuss the contents of the booklet with him. Assure the patient that you will be happy to speak with her partner and answer any questions he may have about her Accutane treatment and the need to use two separate, effective forms of contraception during the required period. An alternative to an office visit by the partner may be a telephone call to your office, or written or e-mailed questions. This may be a good time to tell your patient about the Confidential Contraception Counseling Line. The toll-free number is 1-800-542-6900.

Selecting Contraception¹

Asking the patient about her choice of contraception takes special skill, and you may wish to refer your female patients to a reproductive health and contraception counselor. You may use the Roche-supported free referral in order to accomplish this goal; however, if you wish to assess your patient's attitudes and beliefs for yourself, you may wish to follow the advice.

Patients should be asked as discreetly as possible, "Have you ever had or are you currently having sexual intercourse, sex play or oral sex with a male partner?" It is not unusual to have a patient indicate that she is practicing abstinence; however, through questioning the prescriber may find out, for example, that the patient is practicing abstinence because her sexual partner is away. Continuous abstinence is only a description of her history—not an indication of her future. Remember that the patient's situation may change. Abstinence means no sexual contact. A patient needs to understand that pregnancy is possible if semen or pre-ejaculate is spilled on the vulva. The effectiveness of abstinence cannot be determined because it exists only when it is practiced.

Because it is not possible to measure contraceptive effectiveness directly, the prescriber can evaluate probabilities of pregnancy during contraceptive use. These are obtained from surveys as well as research studies.

The percentages that follow for the perfect use and typical use of a contraceptive indicate the percentages of women experiencing an unintended pregnancy during their first year of use. Perfect use describes the use of the method correctly and consistently with every act of intercourse. Typical use reflects the average user, who does not always use the method correctly and consistently, and may not use it with every act of intercourse.

Primary (Most Effective) Forms of Contraception

ORAL CONTRACEPTION <i>(Rate of unintended pregnancies)</i>	Perfect Use: 0.1% Typical Use: 5%
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Combination Oral Contraceptives

(estrogen and progestin available in a variety of formulations)⁷

Mechanism of Action — ovulation suppression.

Instructions for Use — take pill at same time daily —hormone pills for 3 weeks; placebos for 1 week.

Pills containing no estrogen (progestin-only "minipills") are not recommended during Accutane therapy.

If the Pill is recommended for your patient as the primary method, she must also use a secondary method at all times.

IMPLANTABLE HORMONES <i>(Rate of unintended pregnancies)</i>	Perfect Use: 0.05% Typical Use: 0.05%
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Norplant

progestin only — levonorgestrel implants

Mechanism of Action— suppresses ovulation in 50% of cycles, thickens cervical mucus, and atrophies endometrium.

Instructions for Use— 6 capsules inserted by clinician subdermally in upper arm; must be replaced every 5 years.

If Implantable Hormones are recommended for your patient as the primary method, she must also use a secondary method at all times.

INJECTABLE HORMONES <i>(Rate of unintended pregnancies)</i>	Perfect Use: 0.3% Typical Use: 0.3%
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Depo-Provera

progestin-only injection

Mechanism of Action— suppresses ovulation; thickens cervical mucus; atrophic endometrium.

Instructions — receive injection every 12 weeks (150 mg/1 cc IM).

Lunelle

combination hormone (estrogen + progestins) injection

Mechanism of Action— similar to that of Depo-Provera

Instructions for Use— receive injection every 4 weeks (28 to 33 days).

If Injectable Hormones are recommended for your patient as the primary method, she must also use a secondary method at all times.

INTRAUTERINE DEVICE (IUD) <i>(Rate of unintended pregnancies)</i>	Perfect Use: 0.1%-1.5% Typical Use: 0.1%-2%
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IUD

Description— 3 types used in the US:

CuT 380A — made of polyethylene covered with copper;

Progesterone T — made of ethylene vinyl acetate copolymer containing progesterone;
 LNg20 — made of polyethylene and containing levonorgestrel.

Mechanism of Action—CuT 380A — prevents fertilization by altering tubal and uterine transport of sperm; Progesterone T and LNg20 — release progesterone, which alters uterine and tubal motility, thickens cervical mucus, alters endometrium, and disrupts ovulatory patterns.

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Instructions for Use — patient should check for IUD strings often in the first few months after insertion and after each period. If the patient cannot find the strings or if strings feel shorter or longer, or if she can feel the IUD itself, or if there are any signs or symptoms of pelvic inflammatory disease (PID) or if she misses a period, instruct the patient to call her prescriber.

If the IUD is recommended for your patient as the primary method, she must also use a secondary method at all times.

STERILIZATION <i>(Rate of unintended pregnancies)</i>	Perfect Use: 0.5% Typical Use: 0.5%
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Female Sterilization

Mechanism of Action— prevents fertilization by mechanically blocking fallopian tubes.

Male Sterilization (Vasectomy)

Mechanism of Action— prevents sperm from entering the seminal fluid by blocking the vasa deferentia, semen analysis advised after 20 ejaculations to be sure semen is free of sperm.

If Sterilization is your patient’s primary method, she must also use a secondary method at all times.

Secondary (Moderately Effective) Forms of Contraception

Condoms, diaphragms and cervical caps are barrier methods that are considered moderately effective.

CONDOMS <i>(Rate of unintended pregnancies)</i>	Perfect Use: 3% with spermicide Typical Use: 14% with spermicide
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Male Condom (Latex)

Mechanism of Action— prevents sperm from entering vagina.

Instructions for Use— unroll the condom on to erect penis before there is any contact with female genitals; use only water-based lubricants with latex condoms.

If the Condom is one of your patient's methods of contraception, she must also use a primary method at all times.

DIAPHRAGM <i>(Rate of unintended pregnancies)</i>	Perfect Use: 6% with spermicide Typical Use: 20% with spermicide
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Diaphragm

Description— dome-shaped rubber cup with a flexible rim available in many (50-95 mm diameter) and different styles.

Mechanism of Action— acts as a physical barrier to prevent sperm from entering cervix and contains spermicide to kill sperm (may help to hold spermicide against cervix)

If the Diaphragm is one of your patient's methods of contraception, she must also use a primary method at all times.

CERVICAL CAP <i>(Rate of unintended pregnancies in nulliparous women)</i>	Perfect Use: 9% with spermicide Typical Use: 20% with spermicide
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Cervical Cap

Description— deep rubber cap with firm rim and a groove inside the rim that fits snugly around the cervix.

Mechanism of Action— acts as a physical barrier to prevent sperm from entering cervix and uses chemical action of spermicide to kill sperm.

If the Cervical Cap is one of your patient's methods of contraception, she must also use a primary method at all times.

WITHDRAWAL OR PERIODIC ABSTINENCE ARE NOT RECOMMENDED FOR WOMEN TAKING ACCUTANE

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Emergency Contraception⁷

Types of Emergency Contraception

Emergency birth control is provided in one of two ways: emergency contraception pills, or insertion of an IUD.

EMERGENCY CONTRACEPTION PILLS (ECPs) —Used within 3 days of unprotected sexual intercourse

Emergency hormonal contraception is a sequence of high doses of certain oral contraceptives. **The first dose of the ECPs must be taken no later than 72 hours after having unprotected sex.** The sooner the ECP is taken, the more likely it is to be effective.

INSERTION OF INTRAUTERINE DEVICE (IUD)—Used within 5 days of unprotected sexual intercourse

The second method used for emergency contraception is the insertion of an IUD. Insertion of an IUD can be done by a healthcare professional within 5 days of unprotected sex.

IUD insertion for emergency contraception is not recommended for women who have not had a child, or are at risk for sexually transmitted infections. This includes:

- Women with more than 1 sex partner or whose partners have more than 1 partner
- Women with new partners
- Women who have been raped

The names and phone numbers of emergency contraception prescribers in your area can be obtained by calling toll free: 1-888-NOT-2-LATE (1-888-668-2528).

Informed Consent

3. Female patients 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.

Signing the informed consent provided in the female booklet allows an opportunity for you to review that she has the ability to read and understand the information that you have given her and that she understands her responsibilities to avoid pregnancy before, during and for one month after Accutane therapy.

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The Accutane Survey

4. Female patients must have been informed of the purpose and importance of participating in the Accutane Survey and have been given the opportunity to enroll.

The Accutane Survey is conducted independently by the Slone Epidemiology Unit of the Boston University School of Public Health. Patients will receive a payment for enrolling—it is important that ALL female patients who use Accutane enroll in this survey.

The Accutane Survey is a large epidemiologic study of women who have taken Accutane. Data from this Survey are reported to the FDA and are used to assess the effectiveness of S.M.A.R.T. Roche also uses the data to evaluate possible ways to further reduce fetal exposure.

This confidential survey collects information from patients on their understanding of the risks of pregnancy during Accutane therapy, and other aspects of the Accutane Pregnancy Prevention Risk Management Program. After enrollment in the Accutane Survey, female patients will be requested to complete three or four brief questionnaires.

Continue to encourage female patients to enroll at every office visit until they actually do so. Survey enrollment forms are enclosed in each Prescription Pak of Accutane and in each individual patient booklet.

Confidentiality

Information gathered in the Accutane Survey will be used for statistical purposes only and will be held in the strictest confidence. Only the Accutane Survey researchers at Boston University have access to personal patient information.

Payment

An initial payment of \$20 will be made to every female patient who enrolls in the Accutane Survey. An additional payment of \$10 will be made after the patient completes the final questionnaire.

Convenience

Enrollment is simple and convenient for patients. An enrollment form is enclosed in every Prescription Pak of Accutane and in every female patient booklet.

Encouragement

Your encouragement is important to the patient. Patient feedback indicates that patients decided not to enroll because:

- They did not receive information about the survey at their prescriber's office
- They were concerned about their privacy
- They were concerned about the amount of time involved

However, the patients who decided to enroll did so because:

- They felt it would benefit others
- **The prescriber had recommended their participation**

If the patient believed that the prescriber supported the survey, they joined. Please encourage your patients to participate. Assure them that there are only three or four short forms to complete during the entire course of therapy, that their responses are completely confidential, and that they will be compensated for their efforts. Explain to patients that their participation is an important contribution to improving the program for prevention of pregnancies among women taking Accutane.

Reaching the Goal

The importance of enrolling female patients in the Accutane Survey cannot be overstated. Please encourage all of your female Accutane patients to enroll—without exception.

Our objective is clear—the enrollment of every female patient. To reach this goal, we need your support, and your patients need your encouragement.

INSIDE BACK POCKET

To Order Supplies

After you send your S.M.A.R.T. *Letter of Understanding* and have received your initial materials, you can reorder through the phone line.

Services available through the phone line

After you press 1 to select Accutane, the following three branches are available:

- 1 Branch One
 - Overview of the Pregnancy Prevention Program
- 2 Branch Two
 - Contraception counseling reimbursement requests
 - Inquiries about past reimbursement requests
- 3 Branch Three
 - Order Pregnancy Prevention Program materials
 - Inquiries about status of past orders

To place an order by phone:

- Dial 1-800-93-ROCHE (1-800-937-6243)
- Press 1 for Accutane
- Follow the on-line instructions to access Branch 3
- When you have accessed Branch 3, you will be immediately connected with a representative who will process your order. Just give the representative your name and address.

Service representatives are available to assist you from 9 am to 7 pm (EST). At all other times, please leave your name and telephone number. A representative will return your call the next business day.

Please allow 2 to 3 weeks for delivery.

To place an order by mail

If you prefer to order additional Pregnancy Prevention Program materials by mail, please use the reorder card enclosed with every S.M.A.R.T. *Guide to Best Practices*. When ordering by mail, please allow 6 to 8 weeks for delivery.

***NOTE: COMPONENTS TO BE INSERTED INTO BACK POCKET:
System to Manage Accutane Related Teratogenicity Letter of Understanding
Full Product Information***

BACK COVER:

**Table of Contents
Where to find information.**

Female Patients	Finding the information	On Page	
<p>Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first five 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. The manufacturer will make available urine pregnancy test kits for female Accutane patients for the initial, second and monthly testing during therapy.</p>	<p><i>S.M.A.R.T. Guide to Best Practices</i></p> <p><i>Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women</i></p>	<p>Contraception Algorithm, inside back pocket</p> <p><i>S.M.A.R.T. Letter of Understanding</i>, inside back pocket</p> <p>Patient Product Information, Section 1: Education, page 3</p> <p>Contraception Counseling Referral Form, Section 1: Education</p> <p>Patient Information/Consent Form, Section 2: Consent</p> <p>Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent</p> <p><i>Preventing Pregnancy—A Guide to Contraception</i>, Section 3: Education</p> <p>Reinforcement, page 22</p>	

<p><u>Must</u> have selected and committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of contraception for at least 1 month prior to initiation of Accutane therapy, during 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.</p>	<p>S.M.A.R.T. <i>Guide to Best Practices</i></p> <p><i>Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women</i></p>	<p>S.M.A.R.T. <i>Letter of Understanding</i>, inside back pocket</p> <p>Contraception Counseling Referral Form, Section 1: Education Patient Product Information, Section 1: Education Patient Information/Consent Form, Section 2: Consent Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent <i>Preventing Pregnancy—A Guide to Contraception</i>, Section 3: Education Reinforcement, page 22</p>
<p><u>Must</u> have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.</p>	<p>S.M.A.R.T. <i>Guide to Best Practices</i></p> <p><i>Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women</i></p>	<p>S.M.A.R.T. <i>Letter of Understanding</i>, inside back pocket</p> <p>Patient Information/Consent Form, Section 2: Consent Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent Informed Consent/Patient Agreement, Section 2: Consent</p>

<p><u>Must</u> have been informed of the purpose and importance of participating in the Accutane Survey and have been given the opportunity to enroll.</p>	<p>S.M.A.R.T. <i>Guide to Best Practices</i></p> <p><i>Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women</i></p>	<p>S.M.A.R.T. <i>Letter of Understanding</i>, inside back pocket</p> <p>Accutane Survey Enrollment Form, Section 2: Consent Patient Information/Consent Form, Section 2: Consent Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent <i>Preventing Pregnancy—A Guide to Contraception</i>, Section 3: Education Reinforcement, page 21</p>
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References: 1. Trussell J, Card JJ, Rowland Hogue CJ. Adolescent sexual behavior, pregnancy, and childbearing. In: Hatcher RA, Trussell J, Stewart F, et al, eds. *Contraceptive Technology*. 17th ed. New York, NY: Ardent Media, Inc.; 1998:701-744. 2. Dai WS, Hsu M-A, Itri LM. Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol*. 1989;125:362-365. 3. Brunton SA. Physicians as patient teachers. *West J Med*. 1984;141:855-860. 4. Meichenbaum D, Turk DC. *Facilitating Treatment Adherence*. New York, NY: Plenum Press; 1987: chap 2-5. 5. Terry K. Telling patients more will save you time. *Med Econom*. July 15, 1994;40-52. 6. Lipkin M. The medical interview and related skills. In: Branch WT Jr, ed. *Office Practice of Medicine*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 1987:1287-1306. 7. Planned Parenthood. *Emergency Contraception*. Available at <http://www.plannedparenthood.org/ec/html>. Accessed February 24, 2000.

((ACCUTANE LOGO))

Please see the enclosed complete product information, including boxed CONTRAINDICATIONS AND WARNINGS, in pocket.

((ROCHE LOGO))

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 Plandex XXXX

**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 prescribers to be in compliance with the Accutane package insert approved on October 30, 2001. 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 a 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 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 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 Black Box Warning of the labeling approved October 30, 2001. Specifically, she:

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test should be done during the first five 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 committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis. (See Black Box in the package insert for full information).
- 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).

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 pre-addressed 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.

COLOR = YELLOW

Accutane® Qualification Sticker

Female

Male

Female patient has been qualified as described in Black Box of package insert
on _____

Qualification date

QTXXXXXXXXX DEA# ABXXXXXXXXX

Pharmacist:

- **Fill within 7 days of qualification date**
- **No more than one-month supply ONLY**
- **NO refills allowed**

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TO: Boards of Pharmacy

FROM: Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

DATE: October 30, 2001

RE: Accutane Prescriptions Under the S.M.A.R.T. Program
(System to Manage Accutane Related Teratogenicity)

FDA is addressing this letter to all U.S. boards of pharmacy to signal the launch of the S.M.A.R.T. Program (System to Manage Accutane Related Teratogenicity) on October 30, 2001.

Accutane is a prescription medication manufactured by Hoffmann-La Roche prescribed for the treatment of severe recalcitrant nodular acne that is unresponsive to standard therapies. Accutane presents an extremely high risk of birth defects if taken by a female patient who is pregnant while taking the drug. 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 have been documented. There is an increased risk of spontaneous abortion and premature births.

The S.M.A.R.T. Program is an enhanced risk management program developed and implemented by Hoffmann-La Roche in partnership with the FDA because, despite extensive warnings, women continue to receive Accutane prescriptions when pregnant or become pregnant while taking Accutane.

Safe Prescribing of Accutane Under the S.M.A.R.T. Program

Under the S.M.A.R.T. Program, each patient must be "qualified" by the prescriber to receive Accutane. This qualification signifies that each female patient:

- **Must** have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test should be done during the first five 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 committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms

of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis. (See Black Box) package insert for full information).

- **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.

This qualification by the prescriber will be documented by use of a yellow self-adhesive Accutane Qualification Sticker attached to each prescription blank. Accutane should be dispensed only for prescriptions which bear the yellow self-adhesive Accutane Qualification Sticker.

Qualification Stickers on Accutane Prescriptions

In accordance with the risk management goals of the S.M.A.R.T. Program, prescribers will be required to attach a yellow self-adhesive Accutane Qualification Sticker to all Accutane prescriptions. The Qualification Sticker is sized to fit in the middle of the physician's prescription blank, and once affixed it cannot be removed without destroying the blank. (See enclosed example)

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

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

The Accutane Qualification Stickers will serve as an identifier to pharmacists that the patient has been qualified by the prescriber as an appropriate patient for Accutane therapy. Pharmacists will have the option to verify the authorization for the sticker by calling 1-800-93-ROCHE. This step is not required by pharmacists to be in compliance with S.M.A.R.T.

The requirements of the S.M.A.R.T. Program, as set forth in package insert approved by FDA on October 30, 2001, are designed to prevent pregnancies while on Accutane. Pharmacists can further contribute to the success of this program by encouraging female patients to enroll in the Accutane Survey conducted by the Slone Epidemiology Unit of Boston University School of Public Health. This confidential Survey will collect and analyze data to help Roche and the FDA decide if S.M.A.R.T. is helping to prevent exposure of pregnant women to Accutane. Patients who agree to participate in the Survey will be making a major contribution to public health by helping identify aspects of S.M.A.R.T. that could be improved. A new, voluntary audit of pharmacies by Roche is also planned to assess the use of the yellow self-adhesive Accutane Qualification Stickers. As part of the validation for this component, the audit will be both retrospective and prospective in nature.

We remind you that there is a FDA-approved Medication Guide for Accutane. This Guide contains safety information written for all patients taking Accutane. It must be dispensed with each Accutane prescription, as required by law.

Thank you for your critically important contribution to the safety of patients taking Accutane.

Should you have any questions regarding this communication, please contact Indira Hills, Regulatory Project Manager, at (301) 827-2020.

****NEW DISPENSING PROCEDURES FOR ACCUTANE AS OF (DATE)****

Dear Pharmacist:

This letter contains new dispensing procedures for Accutane as of (DATE).

Accutane causes severe birth defects. Roche Laboratories Inc., working in cooperation with the FDA, has revised the Accutane Pregnancy Prevention Program (PPP) to introduce an enhanced risk management program called the *System to Manage Accutane Related Teratogenicity*[™](S.M.A.R.T.[™]).

Starting on (DATE), process ALL prescriptions for Accutane as follows:

1. Dispense Accutane only upon presentation of a prescription with a yellow self-adhesive Accutane Qualification Sticker that has been completely and correctly filled in by the prescriber (see example in enclosure). Telephone, fax, and computer-generated orders for Accutane are no longer acceptable.
2. Dispense a maximum of a one-month supply of Accutane. Quantities in excess of a one-month supply are not acceptable.
3. Refills are not acceptable. Dispense more Accutane only upon presentation of a new prescription with a yellow self-adhesive Accutane Qualification Sticker.
4. Fill Accutane prescriptions for female patients within 7 days from the date of qualification noted on the yellow self-adhesive Accutane Qualification Sticker. Prescriptions presented more than 7 days from the qualification date are considered expired, and should not be honored.
5. The Medication Guide must be dispensed to every patient with every Accutane prescription, as required by law.
6. If you wish to verify a prescriber's authorization to prescribe Accutane, call 1-800-93-ROCHE. Use the unique identifier number located on each yellow self-adhesive Accutane Qualification Sticker. This verification is not a requirement for dispensing Accutane.

The *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) will be described fully within the boxed Contraindications and Warnings (Black Box) and Precautions sections of the Accutane package insert.

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

What does the Qualification Sticker Signify?

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

- Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25mIU/mL, before the initial Accutane prescription is written. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test

should be done during the first five 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. Pregnancy testing must be repeated monthly prior to the female patient receiving each prescription.

- Must have selected and committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must have used two forms of contraception for at least one month prior to initiation of Accutane therapy, during therapy, and for one month after discontinuing therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.
- Must have signed a Patient Information/Consent form that contains warnings about the risk of birth defects if the fetus is exposed to isotretinoin.
- Must have been informed of the purpose and importance of participating in the Accutane Survey, and have been given the opportunity to enroll.

How is the Qualification Sticker Used?

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

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

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

Thank you for participating in this important risk management initiative. You can further contribute to the success of this program by encouraging all female patients between 12 and 59 years of age irrespective of pregnancy risk to enroll in the Accutane Survey conducted by the Slone Epidemiology Unit of Boston University School of Public Health. This confidential Survey will collect and analyze data to help Roche and FDA decide if S.M.A.R.T. is helping to prevent exposure of pregnant women to Accutane. A new, voluntary audit of pharmacies by Roche is also planned to assess use of the yellow self-adhesive Accutane Qualification Stickers. If you are contacted, please participate in this important public health endeavor.

Sincerely yours,

Russell Ellison, MD
Chief Medical Officer
Roche Laboratories, Inc.
enclosures

****New Prescribing Procedures for Accutane as of (DATE)****

Dear Accutane Prescriber:

Roche Laboratories Inc., working in cooperation with the FDA, has developed the *System to Manage Accutane Related Teratogenicity™(S.M.A.R.T.™)*. S.M.A.R.T. has been developed because data show that despite extensive warnings, pregnant women continue to receive Accutane prescriptions and women continue to become pregnant while taking Accutane.

Therefore it is imperative that female patients are *qualified* under S.M.A.R.T. to receive an Accutane prescription. Specifically, they must have:

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

Implementation of S.M.A.R.T. will result in a newly revised professional package insert by **(date)**.

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

The System to Manage Accutane Related Teratogenicity (S.M.A.R.T.)

S.M.A.R.T. will be described fully within the boxed Contraindications and Warnings (Black Box) and the Precautions sections of the Accutane package insert. The following list is the necessary steps prescribers must take to be in compliance with the risk management components of the newly revised Accutane package insert.

To receive the first shipment of Accutane Qualification Stickers:

1. **Read the *S.M.A.R.T.™Guide to Best Practices*** (enclosed)
2. **Sign and return**, in the postage paid envelope provided, **the completed *S.M.A.R.T. Letter of Understanding*** (enclosed), which states:
 - 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 a month after stopping Accutane. I will either refer for expert, detailed pregnancy prevention counseling and prescribing

OR I have the expertise to perform this function and elect to do so, before beginning treatment of female patients with Accutane,

- 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 and promotion of the Accutane Survey.

Additional Stickers can then be obtained as needed by calling 1-800-93-ROCHE (details below)

Prior to writing the Accutane prescription:

Obtain screening and confirmation pregnancy tests for ALL female patients. Ensure each female patient is *qualified* according to criteria identified in the Boxed Warning of the package insert.

Monthly visits:

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

Details of S.M.A.R.T. components:

Criteria for Female Patient Qualification:

Female patients of childbearing potential must meet specific criteria to be qualified to receive an Accutane prescription every month she is on Accutane treatment. These criteria are found in the Black Box warning of the package insert. For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies that she:

- **Must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test should be done during the first five 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. Pregnancy testing must be repeated monthly prior to the female patient receiving each prescription.**
- **Must have selected and has committed to use two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use two forms of effective contraception for at least one month prior to initiation of Accutane therapy, during Accutane therapy, and for one 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 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 two 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

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

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

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

Accutane Qualification Stickers

Prescribers must obtain yellow self-adhesive Accutane Qualification Stickers designed to adhere to the center portion of the patient's Accutane prescription (see enclosed example). The Accutane Qualification Stickers can only be obtained by reading the *S.M.A.R.T. Guide to Best Practices* and signing and returning the completed *S.M.A.R.T. Letter of Understanding*. The Guide and the letter are enclosed. Additional Accutane Qualification Stickers can be obtained by calling toll-free at 1-800-93-ROCHE. This number is also found in the Guide.

These Accutane Qualification Stickers will serve as documentation to pharmacists that the patient has been qualified by the prescriber as an appropriate patient for Accutane therapy. Pharmacists will have the option to verify the authorization for the Sticker by calling 1-800-93-ROCHE, but this step is not required. Accutane prescriptions for female patients of childbearing potential should not be filled more than seven days after patient qualification.

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

S.M.A.R.T. outcomes

To measure the effectiveness of S.M.A.R.T., Roche will use several outcome approaches.

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

Continuing Medical Education Credit is Available

Roche has supported a CME program on teratogenic drugs, pregnancy testing, effective contraception, limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure, and methods to evaluate pregnancy risk. To find out how to register for the half-day course, or receive a self-study program, please call 1-800-93-ROCHE.

Thank you for participating in this important risk management initiative. If you have any questions concerning this program please call Roche at 1-800-93-ROCHE.

Sincerely yours,

Russell Ellison, M.D.
Chief Medical Officer
Roche Laboratories, Inc.

Enclosures

((Cover))

patient product information

**important information concerning your treatment with
((accutane logo))**

Read this brochure carefully before you start taking Accutane (ACK-u-tane). This brochure provides important facts about Accutane, but it does not contain all information about this medication. When you pick up your Accutane prescription at the pharmacy, you should receive a copy of the Accutane Medication Guide with your Accutane. If there is anything else you want to know or if you have any questions, talk to your prescriber.

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things you should know about

Accutane is used to treat the most severe form of acne (nodular acne), that has not been helped by other treatments, including antibiotics. However, Accutane can cause serious side effects. Before you decide to take Accutane, you must discuss with your prescriber how bad your acne is, the possible benefits of using Accutane, and its possible side effects. It is important for you to know how to take it correctly and what to expect. Your prescriber will ask you to read and sign a form or forms to show that you understand some of the serious risks of Accutane. Please carefully read this brochure and ask your prescriber if you have any questions.

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

**IMPORTANT INFORMATION FOR FEMALE PATIENTS:
BIRTH DEFECTS**

("Causes Birth Defects")

You **MUST NOT** take Accutane if you are pregnant.

You **MUST NOT** become pregnant while taking Accutane, or for 1 month after you stop taking Accutane.

Severe birth defects are known to occur in babies of females taking Accutane in any amount even for short periods during pregnancy. There is an extremely high risk that your baby will be deformed or will die if you become pregnant while taking Accutane. Potentially any exposed baby can be affected. There is also an increased risk of losing the baby before it is born (miscarriage) or that it will be delivered early (premature).

You will not get your first prescription for Accutane until there is proof you 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 five days of your menstrual period right before starting Accutane therapy, or as instructed by your

prescriber. Only when the 2 required tests show that you are not pregnant can you get your first prescription for a 1-month supply of Accutane. You will have one pregnancy test every month during your Accutane therapy. Female patients cannot get monthly refills for Accutane unless there is proof that they have had a negative pregnancy test. You can only get a refill each month by returning to your prescriber for a repeat pregnancy test and counseling about pregnancy prevention.

Effective contraception (birth control) should be discussed with your prescriber. Two separate, effective forms of contraception must be used at the same time for at least 1 month before beginning therapy and during therapy, and for 1 month after Accutane treatment has stopped. Any birth control method can fail, including oral contraceptives (birth control pills) and injectable (shots)/implantable contraceptive products.

There are only 2 reasons that you would not need to use 2 separate birth control methods:

- You commit to being absolutely and consistently abstinent (no sexual intercourse). This means that you are absolutely sure that you will not have genital-to-genital contact with a male before, during and for 1 month after your Accutane treatment.
- You have had your uterus surgically removed (a hysterectomy).

Immediately stop taking Accutane if you have sex without birth control, miss your period or become pregnant while you are taking Accutane or in the month after you have stopped Accutane treatment. Call your prescriber immediately.

Drawing Showing Some of the Birth Defects

Line drawing representing some common birth defects associated with Accutane use during pregnancy. Some of the defects that you can see are deformed eyes, nose, ears or absent ears, enlarged head and small chin. More severe defects than these can occur including mental retardation. This picture does not show the severe internal defects that may occur including those of the brain, heart, glands, and nervous system.

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important information for all patients

mental disorders and suicide

Some patients have become depressed or developed other serious mental problems while they were taking Accutane or shortly after stopping Accutane. It is not known if Accutane caused these problems. Some signs of depression 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 of ending their own lives (suicidal thoughts). Some people have tried to end their own lives (attempted suicide) and some people have ended their own lives (committed suicide). No one knows if Accutane caused these behaviors.

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

Stop taking Accutane and call your prescriber 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 than usual
- 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 has not been helped by other treatments, including antibiotics.

facts about nodular acne

Nodular acne is a severe skin disease that can leave permanent scars. Although acne is considered by many to be a disease of adolescents, a person can be affected with acne into his or her 30s and 40s. Males tend to get more severe acne than females.

Acne develops in the oil-producing structures of the skin called sebaceous glands. One or more sebaceous glands accompany each hair follicle (see sketch showing typical facial glands associated with acne). These glands secrete an oily mixture called sebum that normally passes to the skin surface. During adolescence, the sebaceous glands grow larger and produce more sebum, especially in the face, chest and back areas. Acne occurs when the normal route of sebum to the skin surface is blocked. In the case of nodular acne, the sebum builds up in the gland and mixes with dead cells. This accumulation finally ruptures the follicle wall, forming an inflamed nodule under the skin. Scarring usually results from these nodules.

Acne is *not* caused by a poor diet, dirt or an oily complexion. Factors that *may make acne worse* include emotional stress, fatigue, cosmetics, and drugs such as iodides and bromides.

((graphic - nodular graphic))

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general guidelines for taking your medication

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. Please carefully read the information included in this brochure, "Important Information for Female Patients: Birth Defects."

Do not take Accutane unless you completely understand its possible risks and are willing to follow all of the instructions in this brochure. When you pick up your Accutane prescription at the pharmacy, you should receive a copy of the Accutane Medication Guide with your Accutane.

Tell your prescriber if you or anyone in your family has had any kind of mental problems, asthma, liver disease, diabetes, heart disease, or any other important health problems. Tell your prescriber if you have any food or drug allergies. This information is important to determine if Accutane is right for you.

how should you take Accutane?

- You will get no more than a 1 month supply of Accutane at a time, to be sure you check in with your prescriber each month to discuss side effects and pregnancy prevention.
- Your prescription should have a yellow self-adhesive Accutane Qualification Sticker on it. If your prescription does not have this sticker, call your prescriber. The pharmacy should not fill your prescription unless it has the yellow sticker.
- The amount of Accutane you take has been specially chosen for you and may change during treatment; do not change the number of pills you are taking unless your prescriber tells you to do so.
- You will take Accutane 2 times a day with food, unless your prescriber tells you otherwise.
- 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 pregnancy test.

during your treatment:

what should you avoid while taking Accutane?

AVOID PREGNANCY (for female patients)
((causes birth defects logo))

- **Do not get pregnant** while 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. 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 may 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.** They may not work while you take Accutane. Ask your prescriber or pharmacist if you are not sure what type of birth control pills 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 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.
- **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.

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important information for all patients

You should be aware that certain **SERIOUS SIDE EFFECTS** have been reported in patients taking Accutane. Serious problems do not happen in most patients. If you experience any of the following side effects or any other unusual or severe problems, stop taking Accutane right away and call your prescriber because they may result in permanent effects.

- **Accutane can cause birth defects and death in babies whose mother took Accutane while they were pregnant.** Please read “Important Information for Female Patients: Birth Defects.”
- **Serious mental health problems.** Please see “Important Information: Mental Disorders and Suicide.”
- **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, and bowel (intestines). 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 or bowel pain, 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. If a bone breaks, tell your prescriber you take Accutane. No one knows if taking Accutane for acne will reduce bone healing or stunt growth.
- **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.

Accutane has more common, 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 side effects usually do not last long and disappear when treatment is stopped, but some may continue after stopping Accutane. If you develop any of these side effects, check with your prescriber to determine if any change in the amount of your medication is needed. Also, ask your prescriber to recommend a lotion or cream if drying or chapping develops.

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.

Be sure to return to your prescriber as scheduled. He or she will want to check your progress with Accutane.

Medicines are sometimes prescribed for purposes other than those listed in this brochure. Patients should ask their prescriber about any concerns. Accutane should not be used for a condition other than that for which it is prescribed.

((page 6))

after your treatment is completed

((causes birth defects logo))

For female patients:

- You must continue using two separate, effective forms of contraception (birth control) for 1 month after your treatment with Accutane has ended. This is because it takes time for all of the Accutane to leave your bloodstream.

For all patients:

- Like most patients, you may find that your skin continues to improve even after completing a course of treatment with Accutane. However, some patients treated with Accutane have needed a second course of therapy for satisfactory results. If this is necessary for you, the second course of therapy may begin 8 or more weeks after the first course.
- Do not donate blood for one month after your treatment with Accutane has ended. This is because it takes time for all of the Accutane to leave your bloodstream.
- Do not give left over Accutane to anyone. It can cause birth defects and other serious health problems.

((accutane logo w/pills))

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((BACK COVER))

((Roche logo w/address))

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Page 1

((Roche logo))

preventing pregnancy A Guide to Contraception

Before, During and After Treatment with Accutane® (isotretinoin)

Complete the Contraception Knowledge Test located in the back of this booklet

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Tab

Introduction

Introduction

Why Is This Information Very Important to Me?

Your dermatologist may prescribe ACCUTANE® (isotretinoin) to be used in your treatment. Accutane is used to treat the most severe form of acne (nodular acne) that has not been helped by other therapies, including antibiotics. Accutane causes severe birth defects. Accutane is indicated only for females who are **not** pregnant. This booklet contains very important facts about Accutane that **you must know and understand before you can begin treatment with Accutane.**

The section of this booklet called **My Role** explains the birth control (contraception) steps you must take before you can start taking Accutane; what you must do during Accutane treatment; and what you must do for 1 month after you stop your Accutane treatment. The severe birth defects that are associated with Accutane use, and the risks that those deformities will occur if Accutane is taken by a woman during pregnancy, are discussed.

Of course, knowing these risks, you will want to avoid becoming pregnant while taking Accutane. To help you, a special Contraception Counseling Referral Program is available from your prescriber that will pay for you to go to another healthcare professional to receive contraception counseling and pregnancy testing. Details of this program are given in the section called **Contraception Counseling Referral Program.**

Many of the ways that will and will not prevent pregnancy are discussed in the section called **Preventing Pregnancy.** Emergency contraception or emergency birth control is used to prevent pregnancy following unprotected intercourse or sex. Details on emergency birth control are provided in the section called **Emergency Contraception.**

Also, it is extremely important that your sexual partner understand that you must use two separate effective methods of birth control for 1 month before, during, and for 1 month after treatment with Accutane. It is very important that your sexual partner understand you must not be pregnant and the special precautions that must be taken during treatment with Accutane and for one month after you completely stop taking Accutane. The section called **Your Sexual Partner** is provided to help you as you talk to your sexual partner about his important role in your treatment with Accutane.

Because you need to understand all the facts in this booklet, read it all the way through. Do **NOT** skip any section of the booklet. After you have read through the booklet once, read it through again. As you read through the second time, write down a list of questions

for your prescriber to answer. Do not worry if you think the question is silly or may be unimportant. You have to understand all the facts in this booklet. Your prescriber wants you to understand everything in this booklet and everything that he or she tells you about Accutane treatment. The facts in this booklet about Accutane and Accutane treatment are very important to your health and well-being.

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My Role

My Role

What Must I Do Before I Can Begin to Take Accutane?

You must receive both oral and written warnings of the risks of taking Accutane during pregnancy and the possibility of birth defects if your unborn baby is exposed to Accutane. You must also sign the Patient Information/Consent Form.

You must use 2 separate, effective methods of birth control at the same time for at least 1 month—BEFORE taking Accutane—even when one is a hormonal contraceptive method.

You must have **negative** results for two pregnancy tests (either blood or urine tests):

- **The first test will be at the time your prescriber decides to prescribe Accutane for you**
- **The second pregnancy test** will be done during the first five days of your menstrual period right before you start taking Accutane, or as directed by your prescriber.

The test measures the amount of a pregnancy hormone you have in your urine or blood. This hormone, called hCG, begins to increase within 48 hours after you become pregnant, but your test may not show a positive result until 7 days later. In order to be very sure that the results are negative and that you are not pregnant, it is important to take the second test when your prescriber tells you to.

These steps must be taken so that you and your prescriber know that you are not pregnant when you begin taking Accutane.

What Must I Do During My Treatment With Accutane?

1. You must return to your prescriber to obtain a new prescription each month.
2. You must be tested for pregnancy each month before you get another prescription for Accutane.
3. **You must** continue to use **2 separate, effective methods** of birth control at the **same time—at all times during your treatment with Accutane** (even when one is a hormonal contraceptive method).

These steps must be taken so that you and your prescriber know you are not pregnant while you are taking Accutane.

You must have the opportunity to join the Accutane Survey. An enrollment form is contained inside this booklet and in the Accutane blister pack. This confidential survey will collect and analyze data to help prevent exposure of pregnant women to Accutane.

Remember: No birth control method will work if you do not use it.

Remember: No birth control method will work if you do not use it correctly and consistently (all the time).

Warning: The effects of alcohol or drugs can impair your judgment, lower your inhibitions and affect your awareness, which can lead to incorrect use of birth control methods.

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My Role

What Must I Do After I Stop Taking Accutane?

You must continue to use 2 separate, effective methods of birth control at the same time for 1 month after stopping Accutane treatment—even when one is a hormonal contraceptive method—because some of the Accutane may remain in your body for this period of time after you stop taking it.

You may be worried about risks to your health with certain birth control methods. It is not unusual for people to have some concerns. You should discuss your concerns about your risks in using the different birth control methods with your prescriber or contraception counselor.

Why Must I Use 2 Separate, Effective Methods of Birth Control?

You must use 2 separate, effective methods of birth control at the same time to prevent pregnancy, because any birth control method can fail and your baby could be born with severe birth defects if you are taking Accutane while you are pregnant.

There is an **extremely high risk** that a deformed baby can result if you become pregnant while taking Accutane in any amount, even for short periods of time. When an unborn baby is exposed to Accutane, there is a higher risk of deformities or a miscarriage. Mothers who were taking Accutane when they got pregnant had deformed infants. This explains the need for the precautions that must be taken before, during and for 1 month after Accutane use. **Remember, not 1 but 2 separate, effective methods of birth control are required while you are taking Accutane.**

What Kinds of Birth Defects Occur With Accutane Use?

Very severe birth defects have occurred with Accutane use including:

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

((Baby defect chart))

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Contraception Counseling Referral Program

Contraception Counseling Referral Program

Be Sure to Ask Your Prescriber About the Contraception Counseling Referral Program

Before you can start taking Accutane, you and your prescriber must be sure that you are not pregnant and that you understand how to avoid becoming pregnant. Because it is so very important that you understand how to avoid becoming pregnant while taking Accutane, a special Contraception Counseling Referral Program has been established by the manufacturer of Accutane.

You or your prescriber can arrange for you to see a contraception counselor who specializes in the female reproductive system. This contraception counselor will provide you with expert counseling about birth control and may even do a pregnancy test.

Even if you feel that you know about birth control, and even if you are not having sex or do not plan to have sex, this counseling is very important in planning your treatment with Accutane. You will not be required to pay for the counseling or any pregnancy testing that they may do. **Be sure to ask your prescriber about the Contraception Counseling Referral Program.**

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Preventing Pregnancy

Preventing Pregnancy

Separating the Myths From the Facts

There are many myths that you may have heard or read about becoming pregnant. These are simply **NOT true**. Here are some of the more common myths and the actual facts.

MYTH (not true): I cannot become pregnant if I am having sex for the first time.

FACT: There is a possibility that you will become pregnant any time that you have sex.

MYTH (not true): I cannot become pregnant if I have sex standing up.

FACT: There is a possibility that you will become pregnant any time that you have sex in any position.

MYTH(not true): I cannot become pregnant if I do not have an orgasm.

FACT: There is a possibility that you will become pregnant any time that you have sex.

MYTH(not true): Douching will keep me from getting pregnant.

FACT: Douching does not prevent pregnancy.

MYTH(not true): I do not have to use birth control every time I have sex.

FACT: Unless you use birth control correctly and every time you have sex, you can become pregnant. You must always follow directions exactly for any method of birth control. If you do not understand a direction completely or you are not absolutely sure about directions, ask your healthcare professional.

MYTH (not true): There is a “safe time of the month” when I cannot become pregnant.

FACT: There is NO safe time. Even fertility awareness methods can fail. You can even become pregnant if you have sex during your menstrual period.

MYTH(not true): I cannot become pregnant if my partner withdraws his penis before he ejaculates or “comes.”

FACT: You can become pregnant even if your male partner ejaculates outside you, away from your vagina. Fluid that contains sperm can leak from the penis before ejaculation. You can get pregnant even if your partner does not enter you, if fluid that contains sperm leaks into you.

MYTH(not true): I cannot become pregnant because I have not started menstruating(my period).

FACT: You will ovulate (release an egg) before your first menstrual cycle, so you are at risk of becoming pregnant if you have sexual intercourse.

MYTH(not true): I cannot become pregnant if I have sex underwater.

FACT: Water does not protect you from becoming pregnant during sexual intercourse.

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MYTH(not true): I cannot become pregnant if I have ovary or womb disease

FACT: There is a possibility that you will become pregnant any time that you have sex.

MYTH (not true): My partner is sterile because he had mumps. He has never gotten anyone else pregnant, so he cannot get me pregnant either.

FACT: Mumps rarely causes sterility, so there is a possibility that you will become pregnant if you have unprotected sex.

MYTH (not true): I cannot get pregnant if I miss only one birth control pill.

FACT: Birth control pills are most effective when taken as prescribed. Their effectiveness may be reduced if the woman misses even one pill.

MYTH(not true): I cannot get pregnant using fertility awareness or natural family planning (having sex only during certain times of the month) if I have regular periods.

FACT: There is no “safe time” for unprotected sex. You may become pregnant any time that you have sex.

MYTH(not true): Sexually active means you have to move during sex—if I do not move, I cannot get pregnant.

FACT: You may become pregnant any time you have sex, whether you move about or lie still during sexual intercourse.

Other: You may have heard or read about something that is not listed here that you think might keep you from becoming pregnant. Be sure to ask your healthcare professional about any method that you cannot find in this book that you think, or have heard, will keep you from becoming pregnant.

How Can I Be 100% Certain That I Will Not Become Pregnant?

Abstinence from sexual intercourse and sexual physical contact 24 hours a day, 7 days a week, is the only way to be 100% sure you will not become pregnant.

What Is Abstinence?

Abstinence means that you have no physical contact of a sexual nature with a male partner. Abstinence is not considered a method of birth control.

Using Abstinence

If you are not currently having any physical contact of a sexual nature with a male partner, it is extremely important that you ask yourself:

Will I definitely remain abstinent while I am taking Accutane?

If your answer is no, talk to your prescriber immediately.

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Preventing Pregnancy

Reasons Women Become Pregnant

It is not unusual for women to become pregnant when they do not wish to be pregnant. But it is **VERY** important that this does not happen to you especially while you are taking Accutane. You must be sure you are not pregnant before, or become pregnant while you are taking Accutane or for 1 month after. Half of all American women at one time or another have experienced a mistimed, unplanned or unwanted pregnancy. And the reasons are very common:

- They were not abstinent
- They chose a birth control method that was not effective
- They did not use birth control every time
- They did not use birth control correctly
- They had unexpected sexual activity
- Their birth control method failed

Be smart—Know the facts

Be safe—Select safe and effective birth control methods

Be sure—Do not leave anything to chance

How Can I Avoid Becoming Pregnant?

Any method of birth control can fail. Even if you use one of the most effective birth control methods correctly, there is still a risk of getting pregnant.

Therefore, 2 separate, effective methods of birth control must always be used together at the same time by female patients starting 1 month before, during, and 1 month after stopping Accutane therapy.

Primary (Most Effective) Methods of Birth Control

At least 1 of the 2 separate methods of birth control must be a primary method of birth control.

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This information does not contain all available information about contraception. As always you should discuss this and any other medical question with your prescriber or contraception counselor.

THE PILL (Oral Contraception)

Two kinds of birth control pills are available and they work in different ways.

Combination pills, which contain 2 hormones, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. In addition, combination pills prevent release of the egg. Your healthcare professional will discuss the different types of pills and help you decide which one is right for you.

Mini-pills, which contain only 1 type of hormone, thicken vaginal mucus to keep the sperm from joining the egg, and may prevent a fertilized egg from attaching to the womb. Mini-pills are not recommended for birth control during Accutane use.

With the Pill method of birth control, 1 pill is taken once a day until the pill-pack is completed. The Pill is usually started the first Sunday after a normal menstrual period or as instructed by your healthcare professional. One pill-pack is completed every menstrual cycle. Not all pills provide protection from the start; you can become pregnant during the first week after you start taking the Pill. Pills should be taken at the same time every day, and it may be helpful to use a calendar. Strike an "X" for the first day of a new package of pills, and check each day thereafter.

With **perfect use** (correctly and consistently), about 1 woman in 1000 becomes pregnant. For **typical use** (not always correctly or consistently), the rate is 5 in 100.

The Pill can have a variety of side effects; most are considered minor. Some rare, but serious, health risks do exist, including blood clots, heart attack and stroke. Women who are older than 35 years, who smoke or who are greatly overweight are at greater risk for these side effects, so it is important to discuss these issues with your prescriber.

If a dose of the combination pill is missed, you can take 1 when you realize it and then continue taking the others at their regular time. **If you miss an entire day, it is okay to take 2 pills together if necessary. If you miss taking your pills more than 2 days in a row, you can become pregnant. Do not have sexual intercourse at this time. If you miss more than 2 days, you should call your healthcare professional as soon as you realize it. You are at greatest risk for pregnancy if you start a package late or miss taking pills during the first week of each package.**

Remember: If the Pill is your primary method, you must still use a secondary method at the same time.

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IMPLANTABLE HORMONES

With this birth control method, your healthcare professional puts 6 small rod-shaped capsules under the skin of your upper arm. The procedure is simple and can be done during an office visit. The capsules release small amounts of hormone that stop release of an egg and thicken vaginal mucus to keep sperm from joining the egg. The capsules remain effective for a number of years, and they can be removed by your healthcare professional at any time.

Implantable hormones are convenient, and there is no daily pill to worry about forgetting. Generally, the side effects are similar to those that occur if you take the Pill. There is a small chance of an irritation at the spot where the capsules are implanted. The contraceptive effectiveness of these hormones begins 3 days after being implanted.

With **perfect use**, about 5 women in 10,000 become pregnant.

For **typical use**, the rate is also 5 in 10,000.

Remember: If implantable hormones are your primary method, you must still use a secondary method at the same time.

INJECTABLE HORMONES

This method of birth control is a shot or needle injection of a hormone in your arm or buttocks, given to you by your healthcare professional at specific intervals every 4 to 12 weeks. The hormone shot stops release of the egg, thickens vaginal mucus to keep the sperm from joining the egg, and keeps a fertilized egg from attaching to the womb. Injectable hormones are convenient, and there is no daily pill to worry about forgetting. Generally, the side effects are similar to those that occur if you take the Pill. This form of birth control is reversible, but it may take several months after stopping the shots before you can become pregnant.

With **perfect use**, about 3 women in 1000 become pregnant.

For **typical use**, the rate is also 3 in 1000.

Injectable hormones can take up to 2 weeks to be fully effective; you can become pregnant during these 2 weeks. Patients who have certain illnesses, or a family history of some illnesses, may not be suited for this type of birth control, so it is important to discuss these issues with your healthcare professional.

Remember: If injectable hormones are your primary method, you must still use a secondary method at the same time.

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THE INTRAUTERINE DEVICE (IUD)

The intrauterine device, which is called the IUD, is a plastic device that contains either copper or hormones. Your healthcare professional puts the small plastic IUD in your womb. The copper or hormones in the IUD keep the sperm from joining the egg and prevent a fertilized egg from attaching to the womb.

IUDs that contain hormones can be left in place for between 1 and 5 years. The copper-containing IUDs can be left in place for up to 10 years. Side effects of all types of IUDs

may include increased cramps and heavier and longer periods. Women with new sex partners, women with more than 1 partner, or women whose partners have other partners have an increased chance of tubal infection (which may lead to sterility).

These risks should be discussed with your healthcare professional. He or she will also explain how to check the IUD for proper position by feeling for a “tail” or string in the vagina. If the string cannot be felt, the IUD may have been expelled or dislodged from its proper position and a healthcare professional should be consulted. This method is not recommended for women who have not had a child.

With **perfect use**, about 1.5 women in 100 become pregnant.

For **typical use**, the rate is 2 in 100.

Remember: If an IUD is your primary method, you must still use a secondary method at the same time.

STERILIZATION: TUBAL LIGATION AND VASECTOMY

Sterilization of either a man or woman requires an operation. A tubal tying (ligation) is intended to permanently block a woman’s tubes where the sperm joins with the egg. A vasectomy is intended to permanently block a man’s semen duct that carries sperm. However, it takes 15 to 20 ejaculations to clear sperm from the man’s semen.

You may become pregnant if your male partner has not had two counts in a row that show there are no sperm in the semen. There are no lasting side effects and sterilization has no effect on sexual pleasure. Mild bleeding or infection may occur right after the procedure. Sterilization is intended to be permanent; reversing the operation is very difficult and cannot be guaranteed.

Women or men who choose sterilization must consult with their healthcare professional before resuming unprotected intercourse. With **perfect use**, about 5 women in 1000 (using female sterilization) or 1 woman in 1000 (using male sterilization) become pregnant. For **typical use**, the rates are 5 in 1000 (female) and 1.5 in 1000 (male).

Remember: If sterilization is your primary method, you must still use a secondary method at the same time.

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Secondary (Moderately Effective) Forms of Birth Control

CONDOM, DIAPHRAGM OR CERVICAL CAP

Each of these is called a “barrier” method of birth control. They are used with a special gel called a spermicide. A spermicide is a substance that kills sperm. By itself, it is **NOT** an adequate birth control method for Accutane users. Spermicides come in several forms—creams, jellies, foams and suppositories, which should be applied 10 to 30 minutes before each intercourse.

Spermicide must be applied each time you have sexual intercourse. Your contraception counselor should explain to you exactly how to use the spermicide with the “barrier” method you choose. The barrier method plus the spermicide count as **ONE** of the two effective methods of birth control you must choose before starting Accutane. The diaphragm or cervical cap must be left in place for 6 hours

after your last sexual act. After intercourse, a spermicide has to remain in place for at least 6 to 8 hours, and a woman should not douche or rinse the vagina during this time.

You should understand exactly how to and how not to use barrier methods of birth control. You need to be aware of common mistakes in their use that may result in pregnancy. These barrier methods of birth control are considered less reliable than the other methods discussed above.

CONDOM

((Condom visual))

The condom, also called a “rubber,” is a thin sheath that traps the sperm. Condoms are made of latex, plastic or animal tissue. Condoms, when used properly and consistently, and with a spermicide, can be effective in preventing pregnancy. Latex condoms have also been described as reducing the risk of catching STDs (sexually transmitted diseases), including HIV. Synthetic and natural skin condoms, or those made from the skin of lamb’s intestines, are equally effective at preventing pregnancy. However, natural skin condoms do not protect against STDs.

Proper use of a condom means several things. If you choose this method, it is important to have your contraception counselor explain exactly how to follow these directions. The condom has to have been stored in a cool, dry place and not exposed to heat or pressure. It should be rolled onto the erect penis before any contact with the woman’s genitals. The rolled rim should always remain on the outside of the condom. If the condom has been rolled incorrectly (backward), it should be discarded and replaced with a new one. A 1/2 inch of empty space should be left at the tip, but no air should be trapped. Air at the tip could cause the condom to break.

The condom should be removed immediately after intercourse to prevent spillage of semen. A condom can be used only once. Oil-based lubricants, like petroleum jelly and baby oil, should not be used with a condom. Water-based lubricants are safe to use and will not destroy the condom. Care should be taken to avoid ripping, tearing or slipping off during sexual activity.

With **perfect use**, about 3 women in 100 become pregnant.

For **typical use**, the rate is 14 in 100.

Remember: Condoms should never be used alone without a primary birth control method.

DIAPHRAGM

The diaphragm is a shallow latex cup. Its purpose is to cover the cervix and prevent sperm from passing up into the womb. Because the size around the cervix varies from woman to woman, a diaphragm has to be custom-fit by a healthcare professional. The fit needs to be checked at least once every 2 years, if a weight gain or loss of 10 or more pounds occurs, or after pregnancy or an abortion.

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Preventing Pregnancy

((Diaphragm visual))

The diaphragm can be inserted into the vagina up to 6 hours before sexual intercourse. Spermicide jelly or cream is placed in the diaphragm and around the rim before insertion. Fresh spermicide should be applied with each sexual intercourse or if 6 hours have elapsed before sexual intercourse occurs. The diaphragm should not be removed when spermicide is reapplied. The diaphragm must be left in place for at least 6 hours after the last sexual intercourse; it should not be left in place for longer than a total of 24 hours because of the risk of serious infection (toxic shock syndrome). Once fitted, the diaphragm is inserted into the vagina so that the dome covers the cervix and the rim fits snugly on the vaginal walls.

With **perfect use** (with spermicide), about 6 women in 100 become pregnant.

For **typical use** (with spermicide), the rate is 20 in 100.

Remember: A diaphragm should always be used with spermicide and only as a secondary method. A separate primary method must always be used.

CERVICAL CAP

The cervical cap is a barrier method that must be individually fitted and prescribed by a healthcare provider. The cervical cap is inserted by the female before each sexual intercourse and must be used in combination with a spermicide, to be considered moderately effective as a birth control method. The cervical cap is made of latex and should never be used with an oil-based lubricant, such as petroleum jelly, as this will destroy the cap.

The cervical cap actually fits over the cervix. The cap should be left in place for at least 6 hours after the last sexual intercourse, but not longer than 48 hours because of the risk of toxic shock syndrome. Spermicide is placed in the cap before insertion, but it is best to add more spermicide with each intercourse while the cap is still in place. The cervical cap should not be removed while the spermicide is being reapplied. Inserting and removing the cervical cap can be somewhat more difficult than inserting and removing the diaphragm. However, with sufficient instruction and practice, insertion and removal can usually be accomplished.

With **perfect use**, about 9 women in 100 become pregnant.

For **typical use**, the rate is 20 in 100.

Remember: A cervical cap should always be used with a spermicide and only as a secondary method. A separate primary method must always be used.

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Preventing Pregnancy

Other Contraception Methods

Do not use less effective methods of birth control such as birth control pills without estrogen, natural family planning, fertility awareness, or withdrawal while taking Accutane, a medication that can cause birth defects to your unborn child. Ask your healthcare professional about other contraception methods that you may use or have heard about.

Early Signs of Pregnancy

While you are taking Accutane, you want to be sure that you are not pregnant or do not become pregnant. That is the reason you are using two methods of safe and effective birth control. But any birth control method can fail, so it is important to know the early signs

of pregnancy and report them to your prescriber as soon as possible. If you suspect that you are pregnant, stop taking Accutane immediately and call your prescriber.

Missing your period may be your first sign that you are pregnant—and usually by that time, pregnancy can be confirmed by either a urine or blood test. However, some women do not miss their period early in their pregnancies. This is why it is so important for you to return each month to your prescriber for a pregnancy test before you get your prescription for more Accutane.

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Preventing Pregnancy

These other signs may, or may not, happen. Remember, if you think you might be pregnant, don't guess! Stop Accutane immediately and call your prescriber.

Morning sickness

Pregnant women may feel nauseous or queasy at any time of the day (only about 50% of women have this feeling).

Breast tenderness

Similar to the feeling you may experience during your monthly period, some women experience sore, swollen and tingling breasts during early pregnancy. Usually, this tenderness goes away over time.

Fatigue

Feeling not just sleepy but “bone weary” (as if you have run a marathon) is a strong indicator that you are pregnant.

Frequent Urination

Rising levels of hormones can cause a feeling of congestion and pressure, which results in more trips to the bathroom.

Slight bleeding

About 8 days after pregnancy begins or sometimes at the time of their expected period, some women experience a small amount of bleeding or spotting. Do not mistake this for a regular period—this spotting may be the result of the embryo embedding in the womb.

Darkening of and around the nipples of the breast

This darkening is caused by an increase in hormones. Some women notice a change in the color of their nipples.

Ectopic Pregnancies

Sometimes a pregnancy begins outside of a woman's womb; this is a very serious problem. Call your prescriber or contraceptive counselor immediately if you are experiencing any of the following signs:

Sudden pain or severe cramping in your lower abdomen

Irregular bleeding or spotting with abdominal pain when your period is late

Fainting or dizziness lasting more than a few seconds

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Tab
Preventing Pregnancy

The manufacturer of Accutane has provided free urine pregnancy test kits to your prescriber. If you want to do your own test, ask for the kit. It is important, however, that you do not guess! If you are not sure how to do the test, or how to look at the result, tell your prescriber.

Using Your ProPhase Plus™ Urine Pregnancy Test

((Pregnancy kit visuals))

1. Obtain a pregnancy test kit and a urine cup from your prescriber or nurse.
2. Urinate in the cup provided.
3. Remove the test kit and dropper from the foil pouch.
4. Place test kit on a flat, level surface.
5. Put the small tip of the dropper into the urine and squeeze bulb to draw the urine in.
6. Add 4 drops of urine into space marked "S" (sample).
7. Wait no longer than 5 minutes as the urine is absorbed (waiting longer than 5 minutes may give a false result).
8. Read the results: The C (control) line should always appear. If it does not, repeat using another kit and start again at Step 1. If only the C line appears, the results are negative (not pregnant). If both the T (test) and C lines appear, the results are positive (pregnant).

The ProPhase Plus™ test can give accurate results as early as 7 days following conception, however it is only 99% accurate until the 11th day after conception. If you have any questions about whether or not you are pregnant please speak to your prescriber or contraception counselor. There are other urine pregnancy tests available. Please review and follow specific test instructions on the kit you choose to use.

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Emergency Contraception

Emergency Contraception

What Is Emergency Contraception and How Does It Work?

Emergency contraception (EC), also called emergency birth control, is commonly known as "after sex" or "morning after" contraception. EC is used to prevent pregnancy following unprotected intercourse or sex. EC prevents release of the egg, joining of the sperm and the egg, or implanting of the egg in the womb. EC will not cause an abortion. EC is for use only if a woman is sure she is not already pregnant from an earlier act of intercourse.

When Would You Use Emergency Contraception?

You would use EC:

If you had unprotected sex

If you forgot to take your birth control pills and had sex without using another method of birth control

If you are late for your contraception injection and had sex without using another method of birth control

If your partner's condom broke or slipped off

If your diaphragm or cervical cap slipped out of place or is ripped or split

Emergency contraception is meant only for emergency situations. It is not a replacement or substitute for your usual two methods of birth control. EC is not to be used as birth control because it is not as effective as regular birth control methods. EC should not be used on a regular basis as a replacement for the other birth control methods described.

Where Can You Get Emergency Contraception?

Contact your prescriber immediately if you have had unprotected sex. You can get EC from:

Private doctors or nurse practitioners

Planned Parenthood

Women's health centers

Hospital emergency rooms (unless they are owned by organizations that oppose the use of birth control)

You can get the name and phone number of EC providers nearest you by calling, toll free, the Emergency Contraception Hotline at 1-888-NOT-2-LATE, which in numbers is 1-888-668-2528.

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Emergency Contraception

Types of Emergency Contraception

Emergency birth control is provided in 2 ways: high doses of contraception pills or insertion of an IUD.

EMERGENCY CONTRACEPTION PILLS (ECPs)—used within 3 days

Emergency hormonal contraception is a sequence of high doses of certain oral contraceptives. Your healthcare professional will help you choose the dose and pill that is right for you. **The first dose of the ECPs must be taken no later than 72 hours after having unprotected sex.** The sooner the ECP is taken, the more likely it is to be effective.

INSERTION OF INTRAUTERINE DEVICE (IUD)—used within 5 days

The second method used for emergency contraception is the insertion of an IUD.

Insertion of an IUD can be done by a healthcare professional within 5 days of having unprotected sex. IUD insertion for emergency contraception is not

recommended for women who have not had a child or are at risk for sexually transmitted diseases. Such women include:

Women with new sex partners

Women with more than 1 partner or whose partners have other partners

Women who have been raped

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Tab
Your Sexual Partner

Your Sexual Partner

How Can I Explain the Importance of Preventing Pregnancy While Taking Accutane?

Explain that there is an extremely high risk that a deformed baby will result if you become pregnant or are pregnant while taking Accutane, in any amount, for even short periods of time.

Explain that when an unborn baby is exposed to Accutane, deformities occur in many cases

Make sure that your partner reads about the types of birth defects as described in the **My Role** section of this booklet so that he can understand the severity of these birth defects.

What Should I Tell My Sexual Partner About Accutane Treatment?

It is **strongly recommended** that your sexual partner read this booklet. It is very important that your sexual partner understand **all the facts about the risks of birth defects occurring in female patients who become pregnant during Accutane therapy.**

- Be very specific when you tell your sexual partner about Accutane and birth defects
- Use this booklet to help you discuss Accutane treatment
- Tell your partner how Accutane may be of benefit to you
- Explain what you and he must do to prevent pregnancy if you plan to engage in sexual activities before you start treatment with Accutane
- Identify and use 2 separate, effective methods of birth control at the same time for 1 month before treatment with Accutane

Explain what you and he must do during Accutane treatment: Continue to use 2 separate, effective methods of birth control at the same time during your treatment with Accutane

- Explain what you and he must do for 1 month after stopping Accutane treatment: Continue to use 2 separate, effective methods of birth control at the same time for 1 month after you stop Accutane treatment
- Have your partner watch the video *Be Prepared, Be Protected* with you. This reproductive health and contraception video is available from your prescriber. Take the video home to watch.
- Encourage your sexual partner to make a list of questions for your prescriber to answer. Your sexual partner may want to come with you to speak directly with the prescriber, or he may want to speak with your prescriber on the phone. Your prescriber wants both you and your sexual partner to understand what must be done while you are taking Accutane. Your prescriber will gladly

make arrangements so that all of your questions may be answered and any concerns can be discussed.

((video visual))

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Your Sexual Partner

Confidential Contraception Counseling Line

If you forgot to ask your prescriber important questions about contraception at your appointment, the manufacturer of Accutane has provided a way for you to obtain information about contraception 24 hours a day, 7 days a week. You can call the toll-free number 1-800-542-6900 and follow instructions to get information on a variety of subjects:

1. Birth defects/teratogenicity
2. Birth control
3. Methods of birth control
4. Emergency contraception
5. Pregnancy and pregnancy testing
6. The Accutane Survey

You should always speak to your prescriber about any information you receive from any source; your prescriber is the best source of information for you.

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The Accutane Survey

The Accutane Survey

Lots of women who have taken Accutane have participated in this Survey. Joining the Survey is important because it is one of the only ways we can know how women are doing with contraception and pregnancy prevention. It is an opportunity to help women who take Accutane in the future.

Some women who did not join the Survey had decided against joining because were worried about privacy or they thought the Survey might be too much paperwork or might be like taking a test.

((Survey visual))

Please don't worry: the Survey is absolutely confidential. Only the researchers at Boston University School of Public Health will know your identity, and they **MUST** keep it confidential. You will be asked to complete a form about 3 times during your treatment on Accutane and once afterward. You will be paid for your time when you join and when you finish the Survey.

You will not be asked test-like questions. In fact, the questions are the same kinds of questions that your prescriber or nurses have already asked you. This information will help us learn more about how women can use Accutane safely. The purpose is to find out what you remembered and what you did with the information you were given.

Join today - you can help yourself and you can help others.

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Tab
Patient Information

Patient Information About Accutane

Warning to female patients: "Avoid Pregnancy" "Causes Birth Defects"

You **MUST NOT** take Accutane if you are pregnant.
You **MUST NOT** become pregnant while taking Accutane, or for 1 month after you stop taking Accutane.

Severe birth defects are known to occur in babies of females taking Accutane in any amount even for short periods during pregnancy. There is an extremely high risk that your baby will be deformed or will die if you become pregnant while taking Accutane. Potentially any exposed baby can be affected. There is also an increased risk of losing the baby before it is born (miscarriage) or that it will be delivered early (premature).

You will not get your first prescription for Accutane until there is proof you 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 five days of the menstrual period right before starting Accutane therapy, or as instructed by your prescriber. Only when the 2 required tests show that you are not pregnant can you get your first prescription for a 1-month supply of Accutane. You will have at least one pregnancy test every month during your Accutane therapy. Female patients cannot get monthly refills for Accutane unless there is proof that they have had this pregnancy test and it is negative. You can only get a refill each month by returning to your prescriber for a repeat pregnancy test and counseling about pregnancy prevention.

Effective contraception (birth control) should be discussed with your prescriber. Two separate, effective forms of contraception must be used at the same time for at least 1 month before beginning therapy and during therapy, and for 1 month after Accutane treatment has stopped. Any birth control method can fail, including oral contraceptives (birth control pills) and injectable (shots)/implantable contraceptive products.

There are only 2 reasons that you would not need to use 2 separate birth control methods:

- You commit to being absolutely and consistently abstinent (no sexual intercourse). This means that you are absolutely sure that you will not have genital-to-genital contact with a male before, during and for 1 month after your Accutane treatment.
- You have had your uterus surgically removed (a hysterectomy).

Immediately stop taking Accutane if you have sex without birth control, miss your period or become pregnant while you are taking Accutane or in the month after you have stopped treatment. Call your prescriber immediately.

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There are other potentially serious side effects of Accutane. These are discussed in the booklet, “*Patient Product Information: Important Facts You Should Know About Your Treatment with Accutane*”. You should also read the Accutane Medication Guide that should be given to you by your pharmacy every time you pick up your Accutane prescription.

SUMMARY:

If you want to be treated with Accutane, there are certain things you **MUST** do:

Before You Take Accutane

You must use 2 separate, effective methods of birth control at the same time for 1 month—before taking Accutane (even when one is a hormonal contraceptive method).

You must have negative results for 2 pregnancy tests:

- **The first test will be done at the time your prescriber decides to prescribe Accutane for you.**
- **The second test will be done during the first five days of your menstrual period right before you start your Accutane therapy, or as directed by your prescriber.**

During Accutane Treatment

You must continue to use 2 separate, effective methods of birth control at the same time—at all times during your treatment with Accutane (even when one is a hormonal contraceptive method).

You must return to your prescriber and have a negative pregnancy test each month before you get your prescription.

You must have the opportunity to join the Accutane Survey. You may find the enrollment form in this booklet or in your medication package.

After Stopping Accutane Treatment

You must continue to use 2 separate, effective methods of birth control at the same time for 1 month after stopping Accutane treatment (even when one is a hormonal contraceptive method) because some of the Accutane may remain in your body for a short period of time after you stop taking it.

Contraception knowledge: Self- Assessment

There is **ONE** correct answer for each question.

Circle the answer you think is correct and then check below to see if you are right! If you got any of the answers wrong, try reading the booklet again. It is full of a lot of important information and it is common for readers to miss answers and have more questions.

Don't take chances: discuss all of your questions with your prescriber **BEFORE** taking Accutane.

1. Your prescriber tells you it is important for you to participate in a survey. Even though you are told it is confidential, it asks for your name and address. What would you do?
 - a) Ask the prescriber why the information is necessary and then decide whether to participate
 - b) Complete the survey, but put a different name on it
 - c) Answer only the questions that are not personal
 - d) Refuse to participate in the survey

2. Your prescriber tells you that you need to have a pregnancy test before he/she can prescribe Accutane. You would:
 - a) Refuse the test because you know you are not pregnant
 - b) Ask the prescriber to explain why you need the test
 - c) Go to another prescriber
 - d) None of the above

3. Your prescriber tells you that you must use at least one primary form of birth control and one secondary form for 1 month before you can start Accutane®. You are on the pill, but don't know if it is a primary form or secondary form. What would you do?
 - a) Don't worry about it now, because you are not sexually active
 - b) Call your friend because she is on an acne medicine
 - c) Ask the prescriber at the next visit
 - d) Review your booklet, Preventing Pregnancy—A Guide to Contraception, and then speak to your prescriber before having sexual intercourse

4. You are speaking to your prescriber about having your second pregnancy test, so you can start Accutane. You have been on the pill for 1 month, and it is the second day of your period. Three days ago, you and your partner forgot to use a condom when you had intercourse. You should:
 - a) Have the pregnancy test anyway because it will tell you if you are pregnant
 - b) Not worry because you have your period

- c) Tell the prescriber you and your partner forgot to use a condom once
 - d) Not worry because you forgot before and never got pregnant
5. If your two birth control methods are the pill and the diaphragm, and you forgot to take two pills in a row, you should:
- a) Not worry because you are using a diaphragm, too
 - b) Not have intercourse and call your prescriber because you may not be protected from becoming pregnant
 - c) Take the pill two at a time until you catch up
6. The reason you are being asked to use two separate, effective methods of birth control at the same time while on Accutane is:
- a) Accutane works better when combined with birth control
 - b) There is a high risk that your baby will be deformed if you become pregnant
 - c) There is a high risk for multiple births when on Accutane
7. Which of the following is an acceptable combination of birth control methods for someone on Accutane?
- a) Withdrawal and a condom
 - b) Cervical cap and a condom
 - c) IUD and withdrawal
 - d) The pill and a diaphragm with spermicide
8. Which of the following is not one of the acceptable methods of birth control while taking Accutane?
- a) Natural family planning
 - b) Sterilization
 - c) IUD
 - d) Cervical cap
9. An appropriate situation for using emergency contraception is:
- a) As a secondary method of birth control
 - b) Only after a positive pregnancy test
 - c) If the condom slipped off or broke during sex
10. If you have questions about your contraception while you are taking Accutane, you should:
- a) Wait for your next visit and ask your prescriber
 - b) Call your prescriber or access the Confidential Contraception Counseling Line to get your question answered before having sexual intercourse
 - c) Ask a friend or your partner

d) Stop taking your contraceptive and Accutane until your next visit

Answers: 1-a, 2-b, 3-d, 4-c, 5-b, 6-b, 7-d, 8-a, 9-c, 10-b

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((Roche logo with address))

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“Be Smart/Be Safe/Be Sure: Accutane Risk Management Program for Men”

Reproduction Information for Men

Booklets and packages for Accutane include many warnings for female patients that Accutane can cause severe birth defects if a pregnant woman takes Accutane. For this reason, male patients who receive prescriptions for Accutane should never share their medicine with other people. In addition to birth defects, Accutane can cause other serious side effects. Never share Accutane.

Question: Do birth defects happen if men who are taking Accutane father a child?

Answer: Males taking Accutane do have small amounts of the drug in the fluid that surrounds sperm, but many years of safety reporting do not point to a pattern of birth defects caused when Accutane is taken by the father. Potential fathers who are concerned can use a condom during the relatively short Accutane treatment period (15-20 weeks).

Even if a person does not take Accutane, it is important to realize that about 3-5% of all newborns have birth due to other known causes of birth defects.

It is also important to realize that Accutane is a chemical (isotretinoin) related to natural vitamin A and that very small amounts of isotretinoin are formed in our bodies every day when we metabolize vitamin A from our food. People taking Accutane have vastly increased levels of isotretinoin have levels of isotretinoin circulating in their blood. For this reason, **neither males nor females should donate blood while taking Accutane or for a month after stopping Accutane, as the blood levels may be high enough to cause birth defects if the blood is given to a pregnant women.**

Question: Can Accutane cause long-term damage to a male’s ability to have healthy children?

Answer: Studies done in men taking Accutane showed no significant effects on the patients’ sperm. The tests included the amount of sperm, the activity of sperm, and the appearance of sperm.

The “Patient Product Information” at the beginning of this booklet begins with information for women, since birth defects are such a terrible, and preventable, side effect of Accutane. Male patients should note that the brochure then contains information very important for ALL patients. **In addition, male patients should read the Accutane Medication Guide that your pharmacy should give to you each time you pick up an Accutane prescription.**

When your prescriber gives you your Accutane prescription, it should have a yellow self-adhesive Accutane Qualification Sticker on it. This special sticker is part of the

S.M.A.R.T. program (System to Manage Accutane Related Teratogenicity [birth defects]). S.M.A.R.T is designed to prevent unborn babies from being exposed to Accutane, a drug that causes severe birth defects. It is important that ALL prescriptions have this Accutane Qualification Sticker so that pharmacists know patients have been cleared by their prescribers to receive the medicine. If your prescription does not have this yellow self-adhesive sticker, please call your prescriber and ask for a prescription with the yellow self-adhesive sticker. Your cooperation in this effort is a very important contribution to preventing Accutane caused birth defects.

If you have any questions about any of these issues or anything you read in the patient booklets, ask your prescriber.

To summarize:

Never share Accutane with anyone else. Do not donate blood during your Accutane treatment or for one month after stopping Accutane, to give the drug time to leave the bloodstream.

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/s/

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