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NARRATION SCRIPT Revised 2/6/03
FLK100VID
ACCUTANE PREGNANCY VIDEO

Opening Segment

"ACCUTANE® CANNOT BE TAKEN BY WOMEN WHO ARE PREGNANT, BECAUSE ACCUTANE CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.

In this video we will see what can happen to an unborn baby if the baby's mother takes Accutane.

A woman must not take Accutane at any time during pregnancy.

Storyboard P2

Accutane is usually prescribed for males and females to treat the most severe form of acne called nodular acne. This type of acne cannot be cleared up by any other acne treatments, including antibiotic pills. Nodular acne has many red, swollen, tender lumps that form in the skin. These lumps are the size of a pencil eraser or larger and can result in permanent scars if not treated.

Because of serious side effects and birth defects, patients should use Accutane only if other treatments including antibiotic pills have not worked.

Storyboard P3

"FEMALE PATIENTS MUST NOT TAKE ACCUTANE IF THEY ARE PREGNANT, PLAN TO BECOME PREGNANT OR BECOME PREGNANT DURING THERAPY. TO AVOID PREGNANCY, WOMEN MUST USE TWO FORMS OF EFFECTIVE CONTRACEPTION ONE MONTH BEFORE STARTING ACCUTANE, WHILE TAKING ACCUTANE, AND FOR ONE MONTH AFTER STOPPING ACCUTANE UNLESS THEY ARE ABSOLUTELY ABSTINENT, NEVER HAVING SEX, OR HAVE HAD THEIR UTERUS OR WOMB REMOVED".

Storyboard P4

"ACCUTANE CAPSULES BREAK DOWN IN THE BODY AND THE MEDICINE ENTERS INTO THE BLOODSTREAM

Storyboard P5

"AND THE BLOOD IS CARRIED INTO THE PLACENTA WHERE IT REACHES THE UNBORN FETUS.

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The medicine can cause severe birth defects."

Storyboard P6

"It is highly possible that the unborn baby may die because the baby's mother took Accutane."

Storyboard P7

"If the fetus lives, as the fetus develops, several birth defects can begin to take place.

These birth defects may be caused by taking Accutane during pregnancy".

Storyboard P8

"One of these birth defects may be abnormal skull development". "Use of Accutane during pregnancy may cause an under development or over development of the skull".

Storyboard P9

"Development of the ears may also be affected"."The ears may not fully develop if Accutane is used during pregnancy. The outer ear may be deformed and the ear canal may be very small or absent entirely causing deformity".

Storyboard P10

"The eyes also may not develop fully".

"The eye socket may be very small or not develop at all causing facial deformity

Storyboard P11

"As face structure begins to form"

"the fetus can have a flattening of the nose and a twisting of the mouth. These birth defects could happen from using Accutane during pregnancy".

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Storyboard P12

"The baby may also be born with a separation of the roof of the mouth and sometimes the lips which is known as a cleft palate".

Storyboard P13

IN ADDITION TO THE VISIBLE DEFECTS, SEVERAL INTERNAL SERIOUS AND LIFE-THREATENING BIRTH DEFECTS MAY DEVELOP IN THE HEART AND IN THE ENTIRE HEART AND BLOOD FLOW SYSTEM.

One of these defects can include an abnormal heart that has the arteries and veins in the wrong position"

Storyboard P14"

The system that helps to fight infection may also be affected. One of the glands in this system - the thymus gland may not develop and the baby then would have trouble fighting infections." "In addition, another gland -the parathyroid gland may not develop. The parathyroid gland helps the baby to form bones by controlling the amount of calcium in the body.

Storyboard P15

Brain and nervous system defects including an abnormal brain may occur…" OR AN UNDERDEVELOPMENT OF THE BRAIN. IT HAS ALSO BEEN REPORTED THAT SOME CHILDREN HAVE LOW IQ SCORES".

Storyboard P17In summary, taking Accutane during pregnancy can result in any or all of these birth defects:

The skull may over- or under- develop.

FACIAL DYSMORPHIA CAN OCCUR, CAUSING A FLATTENING OF THE NOSE AND DISTORTION OF FACIAL STRUCTURE.

Enlargement of the brain may occur.

Eye sockets may be very small or not develop at all.

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The brain can also under-develop.

Ears may not fully develop.

The thymus gland may not develop, affecting an infant's ability to fight off disease.

Abnormalities in the heart and entire cardiac system can be life threatening.

A cleft palate may form.

Storyboard P18

UNLIKE THE BIRTH DEFECTS THAT ARE SEEN IN THE BABIES WHEN MOTHERS TAKE ACCUTANE, THERE IS NO PATTERN OF BIRTH DEFECTS WHEN FATHERS TAKE ACCUTANE.

But men who take Accutane should be careful in other ways." Men might not realize that they should not donate blood during, and for a period of one month following, the end of their Accutane treatment".

Storyboard P 19

"As discussed earlier, Accutane is carried through the bloodstream and a pregnant woman could, unknowingly accept a blood transfusion from a man or a women who took Accutane. The blood and medicine could then pass into the placenta possibly harming an unborn baby".
Therefore, it is extremely important that both men and women taking Accutane do not donate blood during treatment and for a period of at least one month following the end of their Accutane treatment

Storyboard P 20

"Neither men nor women should *ever* share their Accutane with another woman..."

Storyboard P 21

"...BECAUSE OF THE RISK THAT SHE MAY BE PREGNANT."

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"No one should ever share any medicine with anyone else, because the medicine may harm the other person."

Black Box

YOU MUST NOT BECOME PREGNANT WHILE TAKING ACCUTANE, OR FOR ONE MONTH AFTER YOU STOP TAKING ACCUTANE.

Accutane can cause severe birth defects in babies of women who take it while they are pregnant, even if they take Accutane for only a short time.

There is an extremely high risk that your baby will be deformed or will die if you are pregnant while taking Accutane. Taking Accutane also increases the chance of miscarriage and premature births

Female patients will not get their first prescription for Accutane unless there is proof they have had two 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.

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

WHILE YOU ARE TAKING ACCUTANE, YOU **MUST** USE EFFECTIVE BIRTH CONTROL. **YOU MUST USE 2 SEPARATE, EFFECTIVE FORMS OF BIRTH CONTROL AT THE SAME TIME** FOR AT LEAST ONE MONTH BEFORE

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STARTING ACCUTANE, WHILE YOU TAKE IT, AND FOR ONE MONTH AFTER YOU STOP TAKING IT. YOU CAN EITHER DISCUSS EFFECTIVE BIRTH CONTROL METHODS WITH YOUR PRESCRIBER OR GO FOR A FREE VISIT TO DISCUSS BIRTH CONTROL WITH ANOTHER PHYSICIAN OR FAMILY PLANNING EXPERT. YOUR PRESCRIBER CAN ARRANGE THIS FREE VISIT, WHICH WILL BE PAID FOR BY THE MANUFACTURER.

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

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

IF YOU HAVE SEX AT ANY TIME WITHOUT USING TWO FORMS OF EFFECTIVE BIRTH CONTROL, GET PREGNANT, OR MISS YOUR PERIOD, STOP USING ACCUTANE AND CALL YOUR PRESCRIBER RIGHT AWAY.

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Roche

ACCUTANE®

(isotretinoin)

CAPSULES

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INFORMATION FOR PHARMACISTS:

ACCUTANE MUST ONLY BE DISPENSED:

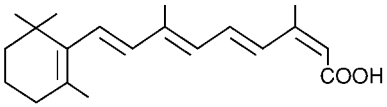
- **IN NO MORE THAN A 30-DAY SUPPLY**
- **ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **WITHIN 7 DAYS OF THE QUALIFICATION DATE**
- **REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER**
- **NO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

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

DESCRIPTION

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

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



CLINICAL PHARMACOLOGY

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

Nodular Acne

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

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Pharmacokinetics

Absorption

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

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

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

*Eating a standardized high-fat meal

Distribution

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

Metabolism

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

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

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

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

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Elimination

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

Special Patient Populations

Pediatric Patients

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

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

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

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

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

INDICATIONS AND USAGE

Severe Recalcitrant Nodular Acne

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

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

CONTRAINDICATIONS

Pregnancy: Category X. See boxed CONTRAINDICATIONS AND WARNINGS.

Allergic Reactions

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

WARNINGS

Psychiatric Disorders

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

Pseudotumor Cerebri

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

Pancreatitis

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

Lipids

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

Blood lipid determinations should be performed before Accutane is given and then at intervals until the lipid response to Accutane is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk during Accutane therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial

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history of lipid metabolism disorder). If Accutane therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS: Laboratory Tests).

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

Hearing Impairment

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

Hepatotoxicity

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

Inflammatory Bowel Disease

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

Skeletal

Bone Mineral Density

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

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lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range –1.6% to -7.6%) in 5 of 8 patients (62.5%).

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

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

Hyperostosis

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

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

Premature Epiphyseal Closure

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

Vision Impairment

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

Corneal Opacities

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

Decreased Night Vision

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

PRECAUTIONS

The Accutane Pregnancy Prevention and Risk Management Programs consist of the *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) and the Accutane Pregnancy Prevention Program

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

The following further describes each component:

1) The S.M.A.R.T. *Guide to Best Practices* includes: Accutane teratogenic potential, information on pregnancy testing, specific information about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy, the methods to evaluate pregnancy risk, and the method to complete a qualified Accutane prescription.
2) The S.M.A.R.T. *Letter of Understanding* attests that Accutane prescribers understand that Accutane is a teratogen, have read the S.M.A.R.T. *Guide to Best Practices,* understand their responsibilities in preventing exposure of pregnant females to Accutane and the procedures for qualifying female patients as defined in the boxed CONTRAINDICATIONS AND WARNINGS.

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

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

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

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

   The booklet for female patients, *Be Smart, Be Safe, Be Sure, Accutane Pregnancy Prevention and Risk Management Program for Women,* also includes a referral program that offers females free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; a second Patient Information/Consent form concerning birth defects, obtaining her consent to be treated within this agreement; an enrollment form for the Accutane Survey; and a qualification checklist

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affirming the conditions under which female patients may receive Accutane. In addition, there is information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, and the rates of possible contraceptive failure; a toll-free contraception counseling line; and patient education videos — the video "Be Prepared, Be Protected" and the video "Be Aware: The Risk of Pregnancy While on Accutane".

General

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

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

Information for Patients and Prescribers

- Patients should be instructed to read the Medication Guide supplied as required by law when Accutane is dispensed. The complete text of the Medication Guide is reprinted at the end of this document. For additional information, patients should also read the *Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin)*. All patients should sign the Informed Consent/Patient Agreement.
- Females of childbearing potential should be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Accutane, while taking Accutane, and for 1 month after Accutane has been stopped. They should also sign a consent form prior to beginning Accutane therapy. They should be given an opportunity to enroll in the Accutane Survey and to review the patient videotapes provided by the manufacturer to the prescriber. The videos include information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a woman who is pregnant takes Accutane at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).
- Accutane is found in the semen of male patients taking Accutane, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.
- Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether or not Accutane therapy is appropriate in this setting (see WARNINGS: Psychiatric Disorders).
- Patients should be informed that they must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events.

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- Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane.
- Patients should be reminded to take Accutane with a meal (see DOSAGE AND ADMINISTRATION). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.
- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.
- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS: Skin and Appendages).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted (see ADVERSE REACTIONS: Musculoskeletal). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see Laboratory Tests: CPK).
- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female than male patients. Arthralgias were experienced in 22% (79/358) of pediatric-patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane. Consideration should be given to discontinuation of Accutane if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported. Accutane should be discontinued if clinically significant decreases in white cell counts occur.

Hypersensitivity

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

Drug Interactions

- *Vitamin A:* Because of the relationship of Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- *Tetracyclines:* Concomitant treatment with Accutane and tetracyclines should be avoided because Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- *Micro-dosed Progesterone Preparations:* Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used combined oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal

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contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see boxed CONTRAINDICATIONS AND WARNINGS).

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

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

Laboratory Tests

Pregnancy Test

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

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

- *Lipids:* Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see WARNINGS: Lipids).
- *Liver Function Tests:* Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS: Hepatotoxicity).

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

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

Pregnancy: Category X. See boxed CONTRAINDICATIONS AND WARNINGS.

Nursing Mothers

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

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Pediatric Use

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

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

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

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

Geriatric Use

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

ADVERSE REACTIONS

Clinical Trials and Postmarketing Surveillance

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

Dose Relationship

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

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Body as a Whole

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

Cardiovascular

palpitation, tachycardia, vascular thrombotic disease, stroke

Endocrine/Metabolic

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

Gastrointestinal

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

Hematologic

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

Musculoskeletal

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

Neurological

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

Psychiatric

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

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

Reproductive System

abnormal menses

Respiratory

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

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Skin and Appendages

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

Special Senses

Hearing

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

Vision

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

Urinary System

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

Laboratory

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

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

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

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

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

OVERDOSAGE

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

Accutane causes serious birth defects at any dosage (see boxed CONTRAINDICATIONS AND WARNINGS). Females of childbearing potential who present with isotretinoin overdose must be

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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Information for Pharmacists

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

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

HOW SUPPLIED

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

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

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

Storage

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

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

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PATIENT INFORMATION/CONSENT (FOR FEMALE PATIENTS CONCERNING BIRTH DEFECTS)

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

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

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

_____
(Patient's Name)

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

   Initial: _____

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

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

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

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

Initial: _____

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

   Initial: _____

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

   Initial: _____

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

    Initial: _____

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

    Initial: _____

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

    Initial: _____

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

    Initial: _____

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

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Initial: _____

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

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

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

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

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

Initial: _____

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

Initial: _____

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

Patient Signature:_____ Date:_____

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

Please print: Patient Name and Address_____
_____ Telephone _____

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

Prescriber Signature: _____ Date:_____

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INFORMED CONSENT/PATIENT AGREEMENT (FOR ALL PATIENTS):

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

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

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

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

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

   Initials: _____

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

   Initials: _____

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

   Initials: _____

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

    Initials: _____

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

    Initials: _____

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

    Initials: _____

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

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Patient Signature: _____ Date: _____

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

Patient Name (print) _____

Patient Address _____ Telephone (___.___.___)

_____

I have:

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

Prescriber Signature: _____ Date:_____

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MEDICATION GUIDE

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

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

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

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

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

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

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

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

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

What are the important warnings for females taking Accutane?

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

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

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must have a negative result from a urine or serum pregnancy test. Female patients cannot get another prescription for Accutane unless there is proof that they have had a negative pregnancy test.

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

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

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

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

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

All patients should read the rest of this Medication Guide.

What are the signs of mental problems?

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

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

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

What is Accutane?

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

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Who should not take Accutane?

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

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

How should I take Accutane?

- You will get no more than a 30-day supply of Accutane at a time, to be sure you check in with your prescriber each month to discuss side effects.
- Your prescription should have a special yellow self-adhesive sticker attached to it. The sticker is YELLOW. If your prescription does not have this yellow self-adhesive sticker, call your prescriber. The pharmacy should not fill your prescription unless it has the yellow self-adhesive sticker.
- The amount of Accutane you take has been specially chosen for you and may change during treatment.
- You will take Accutane 2 times a day with a meal, unless your prescriber tells you otherwise. Swallow your Accutane capsules with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.
- If you miss a dose, just skip that dose. Do **not** take 2 doses the next time.
- You should return to your prescriber as directed to make sure you don't have signs of serious side effects. Because some of Accutane's serious side effects show up in blood tests, some of these visits may involve blood tests (monthly visits for female patients should always include a urine or serum pregnancy test).

What should I avoid while taking Accutane?

- **Do not get pregnant** while taking Accutane. See "What is the most important information I should know about Accutane?" and "What are the important warnings for females taking Accutane?"
- **Do not breast feed** while taking Accutane and for 1 month after stopping Accutane. We do not know if Accutane can pass through your milk and harm the baby.
- **Do not give blood** while you take Accutane and for 1 month after stopping Accutane. If someone who is pregnant gets your donated blood, her baby may be exposed to Accutane and may be born with birth defects.
- **Do not take vitamin A** supplements. Vitamin A in high doses has many of the same side effects as Accutane. Taking both together may increase your chance of getting side effects.
- **Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using Accutane and for at least 6 months after you stop.** Accutane can increase your chance of scarring from these procedures. Check with your prescriber for advice about when you can have cosmetic procedures.
- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. Accutane may make your skin more sensitive to light.

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

What are the possible side effects of Accutane?

Accutane has possible serious side effects

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

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prescriber right away if you have any problems with your vision or dryness of the eyes that is painful or constant.

- **Lipid (fats and cholesterol in blood) problems.** Many people taking Accutane develop high levels of cholesterol and other fats in their blood. This can be a serious problem. Return to your prescriber for blood tests to check your lipids and to get any needed treatment. These problems generally go away when Accutane treatment is finished.
- **Allergic reactions.** In some people, Accutane can cause serious allergic reactions. Stop taking Accutane and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Accutane may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

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

Accutane has less serious possible side effects

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

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

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

Active Ingredient: Isotretinoin.

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

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

R_X only

Roche Pharmaceuticals

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

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((PPP logo))
((Roche Pharmaceuticals logo))

System to Manage Accutane Related Teratogenicity™
S.M.A.R.T.™ Guide
to Best Practices

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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 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. Please refer to the Accutane CONTRAINDICATIONS and WARNINGS and the PRECAUTIONS of the Accutane Product Information.

The following are the CONTRAINDICATIONS and WARNINGS from the approved labeling for Accutane:

((Boxed Copy))
CONTRAINDICATIONS AND WARNINGS: Accutane must not be used by females who are pregnant. Although not every fetus exposed to Accutane has resulted in a deformed child, there is an extremely high risk that a deformed infant can result if pregnancy occurs while taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. Presently, there are no accurate means of determining, after Accutane exposure, which fetus has been affected and which fetus has not been affected.
Major human fetal abnormalities related to Accutane administration in females have been documented. There is an increased risk of spontaneous abortion. In addition, premature births have been reported.
Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia), facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.
Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported.

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Accutane is contraindicated in females of childbearing potential unless the patient meets all of the following conditions:
• Must NOT be pregnant or breast feeding.
• Must be capable of complying with the mandatory contraceptive measures required for Accutane therapy and understand behaviors associated with an increased risk of pregnancy.
• Must be reliable in understanding and carrying out instructions.
Accutane must be prescribed under the System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™).
To prescribe Accutane, the prescriber must obtain a supply of yellow self-adhesive Accutane Qualification Stickers. To obtain these stickers:
1) Read the booklet entitled System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Guide to Best Practices
2) Sign and return the completed S.M.A.R.T. Letter of Understanding containing the following Prescriber Checklist:
• I know the risk and severity of fetal injury/birth defects from Accutane
• I know how to diagnose and treat the various presentations of acne
• I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy
• It is the informed patient's responsibility to avoid pregnancy during Accutane therapy and for 1 month after stopping Accutane. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Accutane I will refer for expert, detailed pregnancy prevention counseling and prescribing, reimbursed by the manufacturer, OR I have the expertise to perform this function and elect to do so
• I understand, and will properly use throughout the Accutane treatment course, the S.M.A.R.T. procedures for Accutane, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Accutane Qualification Stickers
3) To use the yellow self-adhesive Accutane Qualification Sticker: Accutane should not be prescribed or dispensed to any patient (male or female) without a yellow self-adhesive Accutane Qualification Sticker.
For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies that she:
• Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test.
A pregnancy test must be repeated every month prior to the female patient receiving each prescription.
• Must have selected and have committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is

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the chosen method, or the patient has undergone a hysterectomy. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month after discontinuing Accutane therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

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

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception simultaneously. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. These reports occurred while these patients were taking Accutane. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).
Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see precautions).
• Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.
• Must have been informed of the purpose and importance of participating in the Accutane Survey and have been given the opportunity to enroll (see PRECAUTIONS).
The yellow self-adhesive Accutane Qualification Sticker documents that the female patient is qualified, and includes the date of qualification, patient gender, cut-off date for filling the prescription, and up to a 30-day supply limit with no refills.

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

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

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

If a pregnancy does occur during treatment of a woman with Accutane, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to Roche @ 1-800-526-6367 where a Roche Pregnancy Prevention Program Specialist will be available to discuss Roche pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.
Accutane should be prescribed only by prescribers who have demonstrated special competence in the diagnosis and treatment of severe recalcitrant nodular acne, are experienced in the use of systemic retinoids, have read the S.M.A.R.T. Guide to Best Practices, signed and returned the completed S.M.A.R.T. Letter of Understanding, and obtained yellow self-adhesive Accutane Qualification Stickers. Accutane should not be prescribed or dispensed without a yellow self-adhesive Accutane Qualification Sticker.
INFORMATION FOR PHARMACISTS:
ACCUTANE MUST ONLY BE DISPENSED:
• IN NO MORE THAN A 30-day SUPPLY
• ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER
• **WITHIN 7 DAYS OF THE QUALIFICATION DATE**
• REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER

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• 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.
*Females who have had a hysterectomy or who are postmenopausal are not considered to be of childbearing potential.
((End Boxed Copy))

Please see the enclosed complete product information, including CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

((Inside back cover))
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 (isotretinoin), the following seven branches are available:

1. Branch One - Prescribers
   • Inquire about the S.M.A.R.T. Program and obtain Accutane Qualification Stickers

2. Branch Two - Pharmacists
   • Inquire about the S.M.A.R.T. criteria for dispensing Accutane

3. Branch Three - Prescribers, office staff, pharmacists
   • Order materials for the S.M.A.R.T. and Accutane Pregnancy Prevention Programs
   • Inquiries about the status of past orders

4. Branch Four - Contraception counselors
   • Submit reimbursement requests
   • Inquiries about the status of past reimbursement requests

5. Branch Five - Prescribers
   • Hear recorded information about Accutane

6. Branch Six
   • Listen again to the Accutane menu options

7. Branch Seven
   • Return to the main menu

To place an order by phone:
• Dial 1-800-93-ROCHE (1-800-937-6243)
• Press 1 for Accutane

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• 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.

Please see the enclosed complete product information, including CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

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((Back Cover))
((PPP logo))

Where to find information.

((Table, 1st column))

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

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

Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.

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

((Table, 2nd column))

Find the information
S.M.A.R.T. Guide to Best Practices

Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women

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

Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women

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

Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women

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

Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women

((Table, 3rd column))

In Section
S.M.A.R.T. Letter of Understanding, inside back cover

Patient Product Information, Section 1: Education
Contraception Counseling Referral Form, Section 1: Education
Patient Information/Consent Form, Section 2: Consent
Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent
Preventing Pregnancy — A Guide to Contraception, Section 3: Education Reinforcement

S.M.A.R.T. Letter of Understanding, inside back cover
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
Preventing Pregnancy — A Guide to Contraception, Section 3: Education Reinforcement

S.M.A.R.T. Letter of Understanding, inside back cover
Patient Information/Consent Form, Section 2: Consent
Patient Qualification Form for Pregnancy Prevention and Contraception Compliance, Section 2: Consent

S.M.A.R.T. Letter of Understanding, inside back cover
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
Preventing Pregnancy — A Guide to Contraception, Section 3: Education Reinforcement

References: 1. Dai WS, Hsu M-A, Itri LM. Safety of pregnancy after discontinuation of isotretinoin. Arch Dermatol. 1989;125:362-365. 2. Trussell J, Card JJ, Rowland Hogue CJ. Adolescent sexual behavior, pregnancy, and childbearing. In: Hatcher RA, Trussell J,

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Please see the enclosed complete product information, including CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

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((Inside Pages))

((Tab copy))
Facts About Accutane

((PPP logo))

About Accutane

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, suicide, and aggressive and/or violent behaviors); pseudotumor cerebri; pancreatitis; hyperlipidemia; hearing impairment*; hepatotoxicity; inflammatory bowel disease; skeletal changes† (bone mineral density changes, hyperostosis, premature epiphyseal closure); visual impairment (corneal opacities, decreased night vision).
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 posttreatment. Women who become pregnant during this month should be counseled as to the outcome data. In 1989, Dai et al1 reported the results of an epidemiologic study of pregnancies that occurred in women who conceived after discontinuing Accutane. They studied women from 5 days to more 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

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years of postmarketing reports include 4 with isolated defects compatible with features of retinoid-exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.

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.

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.
*No mechanism of action has been established for these events.
†The use of Accutane in patients age 12 to 17 should be given careful consideration, especially when a known metabolic or structural bone disease exists.

Please see the enclosed complete product information, including
CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

((Baby Defect pictures 1))
((caption))

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

((Baby Defect pictures 2))
((caption))

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

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((callouts))

ear abnormalities

parathyroid hormone
deficiency

thymus gland abnormality

cardiovascular abnormalities

Accutane Pregnancy Prevention and Risk Management Program

The Accutane Pregnancy Prevention and 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) The 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 (isotretinoin) 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 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 1 month after stopping Accutane. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Accutane I will refer for

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expert, detailed pregnancy prevention counseling and prescribing, reimbursed by the manufacturer, OR I have the expertise to perform this function and elect to do so
• I understand, and will properly use throughout the Accutane treatment course, the S.M.A.R.T. procedures for Accutane, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Accutane Qualification Stickers
3) 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 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.
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. Thus, ALL prescriptions for Accutane should have the yellow self-adhesive sticker.

((Qualification Sticker and Rx pad art))

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((Tab copy))

Risk Management Program

((PPP logo))

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 2 separate, effective contraceptive methods.

The qualification criteria for female patients are:

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

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

Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner’s

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vasectomy, intrauterine devices, birth control pills, and topical/injectable/ implantable/insertable hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide.

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

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

• Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.

• Must have been informed of the purpose and importance of participating in the Accutane Survey and have been given the opportunity to enroll (see PRECAUTIONS).

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, ie, without using 2 separate effective forms of contraception).

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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.

In a survey conducted in women in the United States, it was reported that approximately 50% of their pregnancies were unintended. Even the most widely used contraceptive, the combination birth control
pill, has a 5% unintended pregnancy rate during the first year of use.

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

Qualification criteria continued on page 5.

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CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

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S.M.A.R.T. Procedures

S.M.A.R.T. is described fully within the 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 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 1 month after stopping Accutane. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Accutane I will refer for expert, detailed pregnancy prevention counseling and prescribing, reimbursed by the manufacturer, OR I have the expertise to perform this function and elect to do so
- I understand, and will properly use throughout the Accutane treatment course, the S.M.A.R.T. procedures for Accutane, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Accutane Qualification Stickers

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 contraindications and warnings 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; phoned, faxed, or electronic prescriptions are not acceptable.
3. Prescribe no more than a 30-day 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.

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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 SI International. 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.

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How to Use the PPP

Be Smart, Be Safe, Be Sure
Accutane Pregnancy Prevention and Risk Management Program for Women

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 (isotretinoin), 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 Be Smart, Be Safe, Be Sure Accutane Pregnancy Prevention and Risk Management Program for Women

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.

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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.

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Obtaining Consent

Accutane Survey Enrollment Form

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An enrollment form for the Accutane Survey, a confidential survey conducted independently by SI International. 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.

((art))

For All Patients: Informed Consent/Patient Agreement

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.

((art))

For Female Patients: Patient Information/Consent

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.

((art))

Patient Qualification Form for Pregnancy Prevention and Contraception Compliance

A form that confirms that a female patient has met the 4 qualification criteria as outlined in the CONTRAINDICATIONS and WARNINGS in the Accutane package insert.

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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.

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Confidential Contraception Counseling Line

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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.

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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.

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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.

((art))

Be Aware: The Risk of Pregnancy While on Accutane

This video provides comprehensive information about types of potential birth defects which could occur if a woman who is pregnant takes Accutane at any time during pregnancy. It is available for you to give to female patients.

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Contraception Knowledge Self-Assessment

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 Preventing Pregnancy—A Guide to Contraception and should be completed by the patient after reading that guide.

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Additional components of the Accutane Pregnancy Prevention and Risk Management Program for Women

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

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Female Qualification Criteria

Meeting the 4 Female Qualification Criteria

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

Pregnancy Testing

Human chorionic gonadotropin (hCG) is a glycopeptide 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.

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	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
	21-28 days postpartum	0

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

Urine Pregnancy Tests

Most urine pregnancy tests that can be used 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 postconception.

A urine pregnancy test with a sensitivity of at least 25 mIU/mL should be utilized. Data from clinical testing by the manufacturer indicate that when directions are followed, barring human error, the tests are 99% accurate.

Assessing Reproductive Health and Contraception Methods Before Prescribing Accutane

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

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.

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

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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 15.2 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, SOCIOECONOMIC STATUS, OR EDUCATION, ALL FEMALES OF CHILDBEARING POTENTIAL MUST HAVE CONTRACEPTION COUNSELING EITHER BY YOU, YOUR STAFF OR THROUGH USE OF THE CONTRACEPTION COUNSELING REFERRAL PROGRAM.

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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

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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 visit[4]
• 35% to 92% of patients will not understand general information given to them[4]
• Prescribers overestimated, by a factor of 9, the amount of time they thought they spent on patient education[5]
• In 65% of the cases, prescribers thought that patients wanted less information than they actually did[5]

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 30-day supply of Accutane (isotretinoin) as provided in the package information with a yellow 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 on 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

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 2 separate, effective forms of contraception simultaneously:

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

Review the Education Reinforcement Section of the patient booklet, Be Smart, Be Safe, Be Sure, including 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 Preventing Pregnancy—A Guide to Contraception section of the Education Reinforcement Section of Be Smart, Be Safe, Be Sure. 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 2 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

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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 2 separate, effective forms of contraception simultaneously, with her sexual partner. Explain and discuss the Preventing Pregnancy—A Guide to Contraception (Your Sexual Partner) section of the Education Reinforcement Section of Be Smart, Be Safe, Be Sure. Encourage her to give the patient booklet to her partner and to discuss the contents 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 2 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.

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Selecting Contraception

Selecting Contraception[2]

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 information provided here.

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	Perfect Use:	0.1%
(Rate of unintended pregnancies)	Typical Use:	5%

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

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IMPLANTABLE HORMONES Perfect Use: 0.05%
(Rate of unintended pregnancies) Typical Use: 0.05%
Norplant® (No longer available to patients after July 2002.)
progestin only — levonorgestrel implants
Mechanism of Action — suppresses ovulation in 50% of cycles, thickens cervical mucus, and atrophies endometrium.
Instruction 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 Perfect Use: 0.2%-0.3%
(Rate of unintended pregnancies) Typical Use: 0.2%-0.3%
Depo-Provera®
progestin-only injection
Mechanism of Action — suppresses ovulation; thickens cervical mucus; atrophies endometrium.
Instructions — receive injection every 12 weeks
(150 mg/1 cc IM).
Lunelle™
combination hormone (estrogen and progestins) injection
Mechanism of Action — similar to that of Depo-Provera.
Instructions — 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) Perfect Use: 0.1%-1.5%
(Rate of unintended pregnancies) Typical Use: 0.1%-2%
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.
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.

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HORMONAL VAGINAL

contraceptive ring	Perfect Use:	0.77%
(Rate of unintended pregnancies)	Typical Use:	1%-2%

NuvaRing®
estrogen (etonogestrel) and progestin (ethinyl estradiol) combination
Mechanism of Action — releases a continuous low dose of hormones per day over a 21-day period of use.
Instructions for use — patient inserts ring in the vagina, where it should remain for 3 weeks; she then removes ring for 1 week, during which she will have her menstrual period. A new ring is used each month for continuous contraception.
If the Hormonal Vaginal Contraceptive Ring is recommended for your patient as a primary method, she must also use a secondary method at all times. A diaphragm cannot be used as a secondary method as the vaginal contraceptive ring may interfere with correct placement and position of the diaphragm.

TOPICAL HORMONAL PATCH

Birth Control Patch	Perfect Use:	1%
(Rate of unintended pregnancies)	Typical Use:	Unknown

Ortho Evra®
norelgestromin/ethinyl estradiol transdermal system
Mechanism of Action — ovulation suppression, and changes in cervical mucous and the endometrium.
Instructions for use — apply a new patch each week for 3 weeks. Every new patch should be applied on the same day of the week. The fourth week is patch-free, during which she will have her menstrual period. The transdermal patch has been found to be less effective in women over 198 pounds. If the patch falls off or is partially detached for less than 24 hours, try to reapply it to the same place or replace with a new patch immediately. This patch should be changed on the usual change day. If the patch is detached for more than 1 day, a new cycle with a new change day should be started by applying a new patch. It will not be effective for contraception for the first week
If the Transdermal Patch is recommended for your patient as the primary method, she must also use a secondary method at all times.

STERILIZATION	Perfect Use:	0.1%-0.5%
(Rate of unintended pregnancies)	Typical Use:	0.15%-0.5%

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

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Condoms, diaphragms and cervical caps are barrier methods that are considered moderately effective when used in combination with a spermicide.

CONDOMS (Rate of unintended pregnancies)	Perfect Use:	3% with spermicide
	Typical Use:	14% with spermicide

Male Condom (Latex)
Mechanism of Action — prevents sperm from entering vagina.
Instructions for Use — unroll condom onto 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 (Rate of unintended pregnancies)	Perfect Use:	6% with spermicide
	Typical Use:	20% with spermicide

Diaphragm
Description — dome-shaped rubber cup with a flexible rim available in many sizes (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 (Rate of unintended pregnancies in nulliparous women)	Perfect Use:	9% with spermicide
	Typical Use:	20% with spermicide

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.

((footnote copy))

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a Wyeth-Ayerst Company.
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Lunelle™ is a trademark of Pharmacia Corporation.
NuvaRing® is a registered trademark of Organon.
Ortho Evra® is a registered trademark of Ortho-McNeil Pharmaceuticals.

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Please see the enclosed complete product information, including CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

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((PPP logo))

Emergency Contraception[7]

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 1 month after Accutane (isotretinoin) therapy.

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 (see precautions).

The Accutane Survey is conducted independently by SI International. Patients will receive a payment for enrolling—it is important that ALL female patients who use Accutane enroll in this survey.

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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 and Risk Management Program. After enrollment in the Accutane Survey, female patients will be requested to complete 2 or 3 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 SI International 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 2 or 3 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.

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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.

Please see the enclosed complete product information, including CONTRAINDICATIONS AND WARNINGS, on the inside back cover.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

I understand that use of the yellow self–adhesive Accutane Qualification Sticker means that a female patient is qualified to receive an Accutane prescription, as defined in the CONTRAINDICATIONS AND WARNINGS of the approved labeling. Specifically, she:
• Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least
11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month prior to the female patient receiving each prescription.

• Must have selected and have committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month after discontinuing Accutane therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.
• Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.

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• Must have been informed of the purpose and importance of participating in the Accutane Survey and given the opportunity to enroll (see PRECAUTIONS).

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

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

Prescriber name (Last) (First) (MI)
DEA number Last four digits of Social Security number
Prescriber address
City
State
Zip code
Telephone
Fax
Prescriber signature Date

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

((Roche Pharmaceuticals logo))
xx-xxx-xxx-xxx-xxxx

((BRM copy))

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 9775 RESTON VA

POSTAGE WILL BE PAID BY ADDRESSEE

System to Manage Accutane® Related Teratogenicity
Program Coordinator
12012 Sunset Hills Rd 8th Fl
Reston VA 20190-9869

NO POSTAGE NECESSARY
IF MAILED
IN THE
UNITED STATES

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NDA 18-882/S048/S052

((PPP Logo))

((Roche Logo))

Be Smart Be Safe Be Sure™
Accutane® Pregnancy Prevention and Risk Management Program for Women

Prevent Pregnancy

IMPORTANT: ACCUTANE CAN CAUSE BIRTH DEFECTS IF TAKEN DURING PREGNANCY.

((Boxed Copy))
If you have any questions about your therapy, please contact:
Name:_____
(to be completed by Prescriber)

Telephone: _____
((End Boxed Copy))

Complete the three sections in this order:

Section 1
Education — Review this material before completing the consent forms
• Patient Product Information, Important information concerning your treatment with Accutane® (isotretinoin)
• Contraception Counseling Referral form

Section 2
Consent — Complete this section with your prescriber
• Accutane Survey enrollment form
• Informed Consent/Patient Agreement form
• Patient Information/Consent form
• Patient Qualification Form for Pregnancy Prevention and Contraception Compliance

Section 3
Education Reinforcement — This additional information will reinforce what you have already learned — complete it in the office or take it home
• Preventing Pregnancy — A Guide to Contraception
  – Introduction
  – My role
  – Contraception Counseling Referral Program
  – Preventing pregnancy
  – Contraception methods
  – Pregnancy and pregnancy testing
  – Emergency contraception

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– Your sexual partner
– The Accutane Survey
– Confidential Contraception Counseling Line
– Accutane InfoLine
– Scenes from the video
– Summary
– Contraception knowledge self-assessment

IMPORTANT INFORMATION TO READ BEFORE YOU RECEIVE YOUR ACCUTANE® (isotretinoin) PRESCRIPTION

((TAB Copy))
section 1
EDUCATION

Tenth Edition
Month/Year

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.

Things you should know about

Accutane (isotretinoin) 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 read this brochure carefully and ask your prescriber any questions you may have.

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

IMPORTANT INFORMATION FOR FEMALE PATIENTS:
BIRTH DEFECTS (Causes Birth Defects)

((Boxed Copy))
You MUST NOT take Accutane if you are pregnant.

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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 that 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 5 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 30-day 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 topical/injectable (shots)/implantable/insertable hormonal birth control 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, 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.

((Illustration of deformed babies))
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 all the severe internal defects that may occur, including those of the brain, heart, glands, and nervous system.
((End Boxed Copy))

Be Aware: The Risk of Pregnancy While on Accutane

A video is available from your prescriber that contains full information about the types of potential birth defects that could occur if a woman who is pregnant takes Accutane at any time during pregnancy.

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((Image of videocassette))

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, 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, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
• Have a change in your appetite or body weight
• Have trouble concentrating
• Withdraw from your friends or family
• Feel like you have no energy
• Have feelings of worthlessness or inappropriate guilt
• Start having thoughts about hurting yourself or taking your own life (suicidal thoughts)

What is Accutane?
Accutane is used to treat the most severe form of acne (nodular acne)
that has not been helped by other treatments, including antibiotics.
((Normal anatomy artwork with Tim Peters copyright line))

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 figures). 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

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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.

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 "Important Information for Female Patients: Birth Defects" on page 1.2.

General guidelines for taking your medication

Do not take Accutane (isotretinoin) 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, osteoporosis (bone loss), weak bones, anorexia nervosa (an eating disorder where people eat too little), 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 a 30-day 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 a yellow sticker.

((Qualification Sticker art))

• The amount of Accutane you take has been specially chosen for you and may change during your 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. Swallow your Accutane capsules with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.
• If you miss a dose, just skip that dose. Do not take 2 doses 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?
DO NOT GET PREGNANT (for female patients)
• Do not get pregnant while taking Accutane and for 1 month after stopping Accutane.

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• 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 light. 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.

Important information for all patients

• Talk with your prescriber 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.
• Talk with your prescriber if you are currently taking an oral or injected corticosteroid or anticonvulsant (seizure) medication prior to using Accutane. These drugs may weaken your bones.
• Do not share Accutane with other people. It can cause birth defects and other serious health problems.
• Do not take Accutane with antibiotics unless you talk to your prescriber. For some antibiotics, you may have to stop taking Accutane until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain.

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 mothers took Accutane while they were pregnant. Please read "Important Information for Female Patients: Birth Defects" on page 1.2.
• Serious mental health problems. Please see "Mental disorders and suicide" on page 1.3.
• Serious brain problems. Accutane can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Accutane and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking Accutane have had seizures (convulsions) or stroke.
• Abdomen (stomach area) problems. Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Accutane. Stop taking Accutane and

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call your prescriber if you get severe stomach, chest, or bowel pain; have trouble swallowing or painful swallowing; get new or worsening heartburn, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine.
• Bone and muscle problems. Accutane may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your prescriber if you plan vigorous physical activity during treatment with Accutane. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are reports that some patients have had stunted growth after taking Accutane for acne as directed. There are also some reports of broken bones or reduced healing of broken bones after taking Accutane for acne as directed. No one knows if taking Accutane for acne will affect your bones. If you have a broken bone, tell your prescriber that you are taking Accutane. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens, stop taking Accutane, and call your prescriber right away.
• Hearing problems. Some people taking Accutane have developed hearing problems.
It is possible that hearing loss can be permanent. Stop using Accutane and call your prescriber if your hearing gets worse or if you have ringing in your ears.
• Vision problems. While taking Accutane you may develop a sudden inability to see in the dark, so driving at night can be dangerous. This condition usually clears up when 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.

After your treatment is completed

• Lipid (fats and cholesterol in blood) problems. Many people taking Accutane (isotretinoin) 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.

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

After your treatment is completed
For female patients:
• You must continue using 2 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 1 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 leftover Accutane to anyone. It can cause birth defects and other serious health problems.

Contraception Counseling Referral Program

Expert Advice At No Cost

((PPP Logo))

Before you can start taking Accutane, you have to be sure that you are not pregnant and that you understand how to avoid pregnancy. That's why Roche Laboratories Inc., the manufacturer of Accutane, will pay for you to go to a contraception counselor. This specialist will provide you with expert counseling about birth control (contraception).
This counseling is very important, even if you already feel you know about birth control, and even if you are not having sex or do not plan to have sex.

6 Simple Instructions

1 Make an appointment to see a contraception counselor and give him/her the attached forms. The counselor should call your prescriber if there are any questions about why
you are there or about how the program works.

2 Notify your prescriber after you have had contraception counseling.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

3 Ask the contraception counselor to mail a copy of the form to your Accutane prescriber.
You will not get your first prescription for Accutane until your prescriber has received this signed form and you have negative results from 2 urine or serum pregnancy tests. Your first test will be obtained as a screening test and the second test will be obtained as a confirmation test during the first 5 days of the menstrual period just before beginning Accutane therapy or as instructed by your prescriber.

4 You must use 2 separate, effective methods of birth control, at the same time, for at least 1 month before treatment, during treatment and for at least 1 month after treatment with Accutane.

5 You are not required to pay any charges for the counseling by the contraception counselor. The counselor should follow the instructions on the attached forms. The fee will be paid by Roche Laboratories Inc.

Accutane Prescriber's Referral Form
((PPP Logo))
Complete for Patients Being Referred for Contraception Counseling.
This patient, _____, is being considered for treatment with Accutane (isotretinoin). She has been referred to you for contraception counseling before she receives a prescription for Accutane.

Accutane is a potent teratogen; therefore, it is essential to rule out pregnancy before her treatment begins and for you to fully inform the patient about effective contraception. The typical course of therapy with Accutane is 15 to 20 weeks in length. The patient must choose 2 separate, effective forms of contraception to be used simultaneously for this period, for at least 1 month preceding and 1 month following therapy. According to the Accutane package insert, the following are considered effective forms of contraception:

Primary: Tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/implantable/insertable hormonal birth control products

Secondary: Diaphragms, latex condoms, and cervical caps: each must be used with a spermicide

The patient must choose at least 1 primary form of contraception.

Please explain the patient's options for contraception, the risk of possible contraceptive failure and the requirements for achieving maximal effectiveness with her chosen methods. Please inform me if the patient does not choose 2 methods of contraception. The patient should also be counseled about emergency contraception.

Therapy cannot begin until pregnancy has been ruled out by negative results from 2 pregnancy tests. The first test is to be done by me as a screening test, and the second test is to be done, as a confirmation test, during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy or, if they have amenorrhea, it should be done at least 11 days after the patient's last unprotected (without using 2 forms of contraception) act of sexual intercourse.

Accutane Prescriber's name_____
(Please affix label, or type or print clearly)

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For current labeling information, please visit https://www.fda.gov/drugsatfda

Address_____
Telephone _____
Accutane Prescriber's signature_____Date_____
Record of contraception counseling to be sent to Accutane prescriber
I have provided the following for your patient _____
(Name)
[] Comprehensive contraception counseling.
[] Information about emergency contraception.
[] The patient has had a negative pregnancy test on _____.
(Date)
The patient has chosen 2 methods of contraception.
[] Yes [] No
Primary method _____
Secondary method _____
Name _____
(Please affix label, or type or print clearly)

Address _____
Telephone _____
Contraception Counselor's signature _____ Date_____

Accutane Prescriber Copy
18-013A-101-008-1102

((NCR FORM [3-part/part 2]))

Accutane Prescriber's Referral Form
((PPP Logo))

Complete for Patients Being Referred for Contraception Counseling.
This patient, _____, is being considered for treatment with Accutane (isotretinoin). She has been referred to you for contraception counseling before she receives a prescription for Accutane.

Accutane is a potent teratogen; therefore, it is essential to rule out pregnancy before her treatment begins and for you to fully inform the patient about effective contraception. The typical course of therapy with Accutane is 15 to 20 weeks in length. The patient must choose 2 separate, effective forms of contraception to be used simultaneously for this period, for at least 1 month preceding and 1 month following therapy. According to the Accutane package insert, the following are considered effective forms of contraception:

Primary: Tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/implantable/insertable hormonal birth control products

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Secondary: Diaphragms, latex condoms, and cervical caps: each must be used with a spermicide

The patient must choose at least 1 primary form of contraception.

Please explain the patient's options for contraception, the risk of possible contraceptive failure and the requirements for achieving maximal effectiveness with her chosen methods. Please inform me if the patient does not choose 2 methods of contraception. The patient should also be counseled about emergency contraception.
Therapy cannot begin until pregnancy has been ruled out by negative results from 2 pregnancy tests. The first test is to be done by me as a screening test, and the second test is to be done, as a confirmation test, during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy or, if they have amenorrhea, it should be done at least 11 days after the patient's last unprotected (without using 2 forms of contraception) act of sexual intercourse.

Accutane Prescriber's name_____
(Please affix label, or type or print clearly)

Address_____
Telephone _____
Accutane Prescriber's signature_____Date_____
Record of contraception counseling to be sent to Accutane prescriber
I have provided the following for your patient _____
(Name)
[] Comprehensive contraception counseling.
[] Information about emergency contraception.
[] The patient has had a negative pregnancy test on _____.
(Date)
The patient has chosen 2 methods of contraception.
[] Yes [] No
Primary method _____
Secondary method _____
Name _____
(Please affix label, or type or print clearly)

Address _____
Telephone _____
Contraception Counselor's signature _____ Date_____

Contraception Counselor Copy
18-013A-101-008-1102

((Back of NCR))

Reimbursement
NOTE: Reimbursement is offered only for contraception counseling. Other services that may be provided during this visit are not eligible for reimbursement.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

The prescriber who actually prescribes Accutane (isotretinoin) is not eligible to use this reimbursement provision.

REIMBURSEMENT INSTRUCTIONS

To receive reimbursement, you must call a toll-free number and enter the designated branch for reimbursement. (If you are calling from a rotary phone, you will be forwarded to an operator who will direct your call.) After you have provided all the requested information, a check will be sent to you by first class mail.

Steps: Dial 1-800-93-ROCHE (1-800-937-6243).

• You will hear recorded instructions on how to obtain reimbursement as a contraception counselor.
• You will be asked to provide the following information:
  - Your name and address
  - Your office phone number
  - Name of graduate school from which you graduated
  - Year of graduation
  - The name and address of the referring Accutane prescriber
  - The patient's name
  - Whether you have provided contraception counseling and information on emergency contraception
  - Your normal and customary charge for providing these services
• You will have an opportunity to record information for up to 5 patients on one call.
• A check will then be processed and mailed to you within 10 days.
• To check on the status of a previous request, you will need only to provide your name, address and phone number. A representative will contact you to update your request status.

NOTE TO CONSULTANTS: By participating in this program you agree to provide Roche with access to additional information should it become necessary to confirm the appropriateness of this request for reimbursement. Roche reserves the right to place limitations on reimbursements or deny reimbursements in certain situations.

((NCR FORM [3-part/part 3]))

Accutane Prescriber's Referral Form
((PPP Logo))

Complete for Patients Being Referred for Contraception Counseling.
This patient, _____, is being considered for treatment with Accutane (isotretinoin). She has been referred to you for contraception counseling before she receives a prescription for Accutane.

Accutane is a potent teratogen; therefore, it is essential to rule out pregnancy before her treatment begins and for you to fully inform the patient about effective contraception. The typical course of therapy with Accutane is 15 to 20 weeks in length. The patient must choose 2 separate, effective forms of contraception to be used simultaneously for this period, for at least 1 month preceding and 1 month following therapy. According to the Accutane package insert, the following are considered effective forms of contraception:

This label may not be the latest approved by FDA.
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Primary: Tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and topical/injectable/implantable/insertable hormonal birth control products

Secondary: Diaphragms, latex condoms, and cervical caps: each must be used with a spermicide

The patient must choose at least 1 primary form of contraception.
Please explain the patient's options for contraception, the risk of possible contraceptive failure and the requirements for achieving maximal effectiveness with her chosen methods. Please inform me if the patient does not choose 2 methods of contraception. The patient should also be counseled about emergency contraception.

Therapy cannot begin until pregnancy has been ruled out by negative results from 2 pregnancy tests. The first test is to be done by me as a screening test, and the second test is to be done, as a confirmation test, during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy or, if they have amenorrhea, it should be done at least 11 days after the patient's last unprotected (without using 2 forms of contraception) act of sexual intercourse.

Accutane Prescriber's name_____
(Please affix label, or type or print clearly)

Address_____
Telephone _____
Accutane Prescriber's signature_____Date_____
Record of contraception counseling to be sent to Accutane prescriber
I have provided the following for your patient _____
(Name)
[] Comprehensive contraception counseling.
[] Information about emergency contraception.
[] The patient has had a negative pregnancy test on _____.
(Date)
The patient has chosen 2 methods of contraception.
[] Yes [] No
Primary method _____
Secondary method _____
Name _____
(Please affix label, or type or print clearly)

Address _____
Telephone _____
Contraception Counselor's signature _____ Date_____

Return this copy to Accutane Prescriber
18-013A-101-008-1102

((Back of NCR))

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Reimbursement
NOTE: Reimbursement is offered only for contraception counseling. Other services that may be provided during this visit are not eligible for reimbursement.
The prescriber who actually prescribes Accutane (isotretinoin) is not eligible to use this reimbursement provision.
REIMBURSEMENT INSTRUCTIONS
To receive reimbursement, you must call a toll-free number and enter the designated branch for reimbursement. (If you are calling from a rotary phone, you will be forwarded to an operator who will direct your call.) After you have provided all the requested information, a check will be sent to you by first class mail.
Steps: Dial 1-800-93-ROCHE (1-800-937-6243).
• You will hear recorded instructions on how to obtain reimbursement as a contraception counselor.
• You will be asked to provide the following information:
- Your name and address
- Your office phone number
- Name of graduate school from which you graduated
- Year of graduation
- The name and address of the referring Accutane prescriber
- The patient's name
- Whether you have provided contraception counseling and information on emergency contraception
- Your normal and customary charge for providing these services
• You will have an opportunity to record information for up to 5 patients on one call.
• A check will then be processed and mailed to you within 10 days.
• To check on the status of a previous request, you will need only to provide your name, address and phone number. A representative will contact you to update your request status.

NOTE TO CONSULTANTS: By participating in this program you agree to provide Roche with access to additional information should it become necessary to confirm the appropriateness of this request for reimbursement. Roche reserves the right to place limitations on reimbursements or deny reimbursements in certain situations.

PLEASE COMPLETE THIS SECTION WITH
YOUR PRESCRIBER OR NURSE

((TAB Copy))
SECTION 2
CONSENT

((SI International Logo))

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Accutane® Survey Enrollment Form – FEMALES ONLY

purpose of the Accutane survey

The Accutane Survey is designed to gather information about how women use Accutane (isotretinoin). The Accutane Survey seeks information on a number of factors including: patient understanding of how Accutane is to be used; previous acne therapy; patient understanding of the hazards of becoming pregnant while taking Accutane; the methods of contraception used during therapy with Accutane; and, if pregnancy occurs, the reason

why and the outcome. The information you provide will help in assessing the System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™) risk management program.

HOW THE ACCUTANE SURVEY WORKS

Your participation is voluntary, but it is important that all female patients who use Accutane enroll in this Survey. Women are asked to complete a few brief questionnaires by mail during and after their Accutane treatment.

CONFIDENTIALITY

SI International conducts the Survey with its clinical consultants. We will keep any information that would identify you strictly confidential. Your confidentiality will be legally protected through a federal Certificate of Confidentiality granted to this Survey.

PAYMENT

To compensate you for participating in the Survey, we will send $20 when you enroll and another $10 when you complete your last questionnaire.

ENROLLMENT

Please complete this form now, seal it, and mail it postage-free today (your prescriber will mail it for you if you'd like). If you prefer to enroll by telephone, please do so by calling 1-888-860-7357.

I agree to participate in the Accutane Survey described above.

Please fold where indicated and glue shut prior to mailing.

(Please print)

Name_____Date of birth_____Sex_____
First Last Month/Day/Year

Street address_____
City_____ State_____ Zip_____
Telephone number_____The best time to reach me by phone_____
Area Code
Prescriber's name_____
First Last

Prescriber's city_____Prescriber's state_____
Month/Day/Year Month/Day/Year

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Date Accutane treatment began_____
Signature_____Date_____

Please be sure that all information is complete.
18-013B-101-008-1102

((BRM Information))

((NCR FORM [2-part/part 1]))

ACCUTANE® (isotretinoin)
Informed Consent/PATIENT AGREEMENT
(for all patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

Read each item below and initial in the space provided if you understand each item and agree to follow your prescriber's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.
Do not sign this agreement and do not take Accutane if there is anything that you do not understand about all the information you have received about using Accutane.

1. I, _____,
(Patient's Name)
understand that Accutane is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.
Initials: _____
2. My prescriber has told me about my choices for treating my acne.
Initials: _____
3. I understand that there are serious side effects that may happen while I am taking Accutane. These have been explained to me. These side effects include serious birth defects in babies of pregnant females. (Note: There is a second Informed Consent form for female patients concerning birth defects.)
Initials: _____
4. I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these behaviors or if they would have happened even if the person

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did not take Accutane. Some people have had other signs of depression while taking Accutane (see #7).
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), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.
Initials: _____
6. Before I start taking Accutane, I agree to tell my prescriber if, to the best of my knowledge, anyone in my family has ever had symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.
Initials: _____
7. Once I start taking Accutane, I agree to stop using Accutane and tell my prescriber right away if any of the following happen. I:
• Start to feel sad or have crying spells
• Lose interest in activities I once enjoyed
• Sleep too much or have trouble sleeping
• Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
• Have a change in my appetite or body weight
• Have trouble concentrating
• Withdraw from my friends or family
• Feel like I have no energy
• Have feelings of worthlessness or inappropriate guilt
• Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
Initials: _____
8. I agree to return to see my prescriber every month I take Accutane to get a new prescription for Accutane, to check my progress, and to check for signs of side effects.
Initials: _____
9. Accutane will be prescribed just for me — I will not share Accutane with other people because it may cause serious side effects, including birth defects.
Initials: _____
10. I will not give blood while taking Accutane or for 1 month after I stop taking Accutane. I understand that if someone who is pregnant gets my donated blood, her baby may be exposed to Accutane and may be born with serious birth defects.
Initials: _____
11. I have read the Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin) and other materials my prescriber gave me containing important safety information about Accutane. I understand all the information I received.
Initials: _____
12. My prescriber and I have decided I should take Accutane. I understand that each of my Accutane prescriptions must have a yellow self-adhesive Accutane Qualification Sticker on it. I understand that I can stop taking Accutane at any time. I agree to tell my prescriber if I stop taking Accutane.
Initials: _____

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

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Patient Signature_____Date_____
Parent/Guardian Signature (if under age 18)_____Date _____
Patient Name (print)_____
Patient Address_____Telephone (____) _____
_____
I have:
• fully explained to the patient,_____, the nature and purpose of Accutane treatment, including its benefits and risks
• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane
• answered those questions to the best of my ability
• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.
Prescriber Signature_____Date_____
Issued: November 2002

Prescriber Copy
18-013C-101-008-1102

((NCR FORM [2-part/part 2]))

ACCUTANE® (isotretinoin)
Informed Consent/PATIENT AGREEMENT
(for all patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

Read each item below and initial in the space provided if you understand each item and agree to follow your prescriber's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.
Do not sign this agreement and do not take Accutane if there is anything that you do not understand about all the information you have received about using Accutane.

1. I, _____,
(Patient's Name)
understand that Accutane is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.
Initials: _____
2. My prescriber has told me about my choices for treating my acne.
Initials: _____
3. I understand that there are serious side effects that may happen while I am taking Accutane. These have been explained to me. These side effects include serious birth defects in babies of pregnant females. (Note: There is a second Informed Consent form for female patients concerning birth defects.)
Initials: _____

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For current labeling information, please visit https://www.fda.gov/drugsatfda

4. I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, “anxious” or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Accutane have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane becoming aggressive or violent. No one knows if Accutane caused these behaviors or if they would have happened even if the person did not take Accutane. Some people have had other signs of depression while taking Accutane (see #7).
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), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.
Initials: _____
6. Before I start taking Accutane, I agree to tell my prescriber if, to the best of my knowledge, anyone in my family has ever had symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.
Initials: _____
7. Once I start taking Accutane, I agree to stop using Accutane and tell my prescriber right away if any of the following happen. I:
• Start to feel sad or have crying spells
• Lose interest in activities I once enjoyed
• Sleep too much or have trouble sleeping
• Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
• Have a change in my appetite or body weight
• Have trouble concentrating
• Withdraw from my friends or family
• Feel like I have no energy
• Have feelings of worthlessness or inappropriate guilt
• Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
Initials: _____
8. I agree to return to see my prescriber every month I take Accutane to get a new prescription for Accutane, to check my progress, and to check for signs of side effects.
Initials: _____
9. Accutane will be prescribed just for me — I will not share Accutane with other people because it may cause serious side effects, including birth defects.
Initials: _____
10. I will not give blood while taking Accutane or for 1 month after I stop taking Accutane. I understand that if someone who is pregnant gets my donated blood, her baby may be exposed to Accutane and may be born with serious birth defects.
Initials: _____
11. I have read the Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin) and other materials my prescriber gave me containing important safety information about Accutane. I understand all the information I received.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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

I now authorize my prescriber _____ to begin my treatment with Accutane.
Patient Signature_____Date_____
Parent/Guardian Signature (if under age 18)_____Date _____
Patient Name (print)_____
Patient Address_____Telephone (____) _____
_____
I have:
• fully explained to the patient,_____, the nature and purpose of Accutane treatment, including its benefits and risks
• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane
• answered those questions to the best of my ability
• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.
Prescriber Signature_____Date_____
Issued: November 2002

Patient Copy
18-013C-101-008-1102

((NCR FORM [2-part/part 1]))

ACCUTANE® (isotretinoin)
PATIENT information/consent
(for all female patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

Read each item below and initial in the space provided if you understand each item and agree to follow your prescriber's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.
Do not sign this agreement and do not take Accutane if there is anything that you do not understand about all the information you have received about using Accutane.

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(Patient's Name)

1. I understand that there is a very high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Accutane in any amount even for short periods of time. This is why I must not be pregnant while taking Accutane.
Initial:
2. I understand that I must not take Accutane (isotretinoin) if I am pregnant.
Initial:
3. I understand that I must not get pregnant during the entire time of my treatment and for 1 month after the end of my treatment with Accutane.
Initial:
4. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) at the same time. The only exception is if I have had surgery to remove the womb (a hysterectomy).
Initial:
5. I understand that birth control pills and topical/injectable/implantable/insertable hormonal birth control products are among the most effective forms of birth control. However, any form of birth control can fail. Therefore, I must use 2 different methods at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is birth control pills or topical/injectable/implantable/insertable hormonal birth control.
Initial:
6. I will talk with my prescriber about any drugs or herbal products I plan to take during my Accutane treatment because hormonal birth control methods (for example, birth control pills) may not work if I am taking certain drugs or herbal products (for example, St. John's Wort).
Initial:
7. I understand that the following are considered effective forms of birth control:
Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills, topical/injectable/implantable/insertable hormonal birth control products, and an IUD (intrauterine device).
Secondary: Diaphragms, latex condoms, and cervical caps. Each must be used with a spermicide, which is a special cream or jelly that kills sperm.
I understand that at least 1 of my 2 methods of birth control must be a primary method.
Initial:
8. I understand that I may receive a free contraceptive (birth control) counseling session from a prescriber or other family planning expert. My Accutane prescriber can give me an Accutane Patient Referral Form for this free consultation.
Initial:
9. I understand that I must begin using the birth control methods I have chosen as described above at least 1 month before I start taking Accutane.
Initial:
10. I understand that I cannot get a prescription for Accutane unless I have 2 negative pregnancy test results. The first pregnancy test should be done when my prescriber decides to prescribe Accutane. The second pregnancy test should be done during the first 5 days of my menstrual period right before starting Accutane therapy, or as instructed by my prescriber. I will then have 1 pregnancy test every month during my Accutane therapy.
Initial:
11. I understand that I should not start taking Accutane until I am sure that I am not pregnant and have negative results from 2 pregnancy tests.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

Initial:
12. I have read and understand the materials my prescriber has given to me, including the Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin). My prescriber gave me and asked me to watch the videos about contraception. I was told about a confidential counseling line that I may call for more information about birth control. I have received information on emergency contraception (birth control).
Initial:
13. I understand that I must stop taking Accutane right away and inform my prescriber if I get pregnant, miss my menstrual period, stop using birth control, or have sexual intercourse without using my 2 methods of birth control at any time.
Initial:
14. My prescriber gave me information about the confidential Accutane Survey and explained to me how important it is to take part in the Accutane Survey.
Initial:
15. I understand that the yellow self-adhesive Accutane Qualification Sticker on my prescription for Accutane means that I am qualified to receive an Accutane prescription, because I:
• have had 2 negative urine or serum pregnancy tests before receiving the initial Accutane prescription. I must have a negative result from a urine or serum pregnancy test repeated each month prior to my receiving each subsequent prescription.
• have selected and committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or I have undergone a hysterectomy. I must use 2 forms of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. I must receive counseling, repeated on a monthly basis, about contraception and behaviors associated with an increased risk of pregnancy.
• have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.
• have been informed of the purpose and importance of participating in the Accutane Survey and given the opportunity to enroll.
My prescriber has answered all my questions about Accutane and I understand that it is my responsibility not to get pregnant during Accutane treatment or for 1 month after I stop taking Accutane.
Initial:

I now authorize my prescriber _____ to begin my treatment with Accutane.
Patient Signature_____Date_____
Parent/Guardian Signature (if under age 18) _____Date_____
Patient Name (print)_____
Patient Address_____Telephone (___) _____
_____
I have:
• fully explained to the patient,_____ , the nature and purpose of Accutane treatment, including its benefits and risks
• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane
• answered those questions to the best of my ability
• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.

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Prescriber Signature_____Date_____
Issued: November 2002

Prescriber Copy
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((NCR FORM [2-part/part 2]))

ACCUTANE® (isotretinoin)
PATIENT information/consent
(for all female patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

Read each item below and initial in the space provided if you understand each item and agree to follow your prescriber's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.
Do not sign this agreement and do not take Accutane if there is anything that you do not understand about all the information you have received about using Accutane.

(Patient's Name)

1. I understand that there is a very high risk that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking Accutane in any amount even for short periods of time. This is why I must not be pregnant while taking Accutane.
Initial:
2. I understand that I must not take Accutane (isotretinoin) if I am pregnant.
Initial:
3. I understand that I must not get pregnant during the entire time of my treatment and for 1 month after the end of my treatment with Accutane.
Initial:
4. I understand that I must avoid sexual intercourse completely, or I must use 2 separate, effective forms of birth control (contraception) at the same time. The only exception is if I have had surgery to remove the womb (a hysterectomy).
Initial:
5. I understand that birth control pills and topical/injectable/implantable/insertable hormonal birth control products are among the most effective forms of birth control. However, any form of birth control can fail. Therefore, I must use 2 different methods at the same time, every time I have sexual intercourse, even if 1 of the methods I choose is birth control pills or topical/injectable/implantable/insertable hormonal birth control.
Initial:
6. I will talk with my prescriber about any drugs or herbal products I plan to take during my Accutane treatment because hormonal birth control methods (for example, birth control pills) may not work if I am taking certain drugs or herbal products (for example, St. John's Wort).

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Initial:
7. I understand that the following are considered effective forms of birth control:
Primary: Tubal ligation (tying my tubes), partner's vasectomy, birth control pills, topical/injectable/implantable/insertable hormonal birth control products, and an IUD (intrauterine device).
Secondary: Diaphragms, latex condoms, and cervical caps. Each must be used with a spermicide, which is a special cream or jelly that kills sperm.
I understand that at least 1 of my 2 methods of birth control must be a primary method.
Initial:
8. I understand that I may receive a free contraceptive (birth control) counseling session from a prescriber or other family planning expert. My Accutane prescriber can give me an Accutane Patient Referral Form for this free consultation.
Initial:
9. I understand that I must begin using the birth control methods I have chosen as described above at least 1 month before I start taking Accutane.
Initial:
10. I understand that I cannot get a prescription for Accutane unless I have 2 negative pregnancy test results. The first pregnancy test should be done when my prescriber decides to prescribe Accutane. The second pregnancy test should be done during the first 5 days of my menstrual period right before starting Accutane therapy, or as instructed by my prescriber. I will then have 1 pregnancy test every month during my Accutane therapy.
Initial:
11. I understand that I should not start taking Accutane until I am sure that I am not pregnant and have negative results from 2 pregnancy tests.
Initial:
12. I have read and understand the materials my prescriber has given to me, including the Patient Product Information, Important Information Concerning Your Treatment with Accutane® (isotretinoin). My prescriber gave me and asked me to watch the videos about contraception. I was told about a confidential counseling line that I may call for more information about birth control. I have received information on emergency contraception (birth control).
Initial:
13. I understand that I must stop taking Accutane right away and inform my prescriber if I get pregnant, miss my menstrual period, stop using birth control, or have sexual intercourse without using my 2 methods of birth control at any time.
Initial:
14. My prescriber gave me information about the confidential Accutane Survey and explained to me how important it is to take part in the Accutane Survey.
Initial:
15. I understand that the yellow self-adhesive Accutane Qualification Sticker on my prescription for Accutane means that I am qualified to receive an Accutane prescription, because I:
• have had 2 negative urine or serum pregnancy tests before receiving the initial Accutane prescription. I must have a negative result from a urine or serum pregnancy test repeated each month prior to my receiving each subsequent prescription.
• have selected and committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or I have undergone a hysterectomy. I must use 2 forms of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. I must receive counseling,

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repeated on a monthly basis, about contraception and behaviors associated with an increased risk of pregnancy.
• have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.
• have been informed of the purpose and importance of participating in the Accutane Survey and given the opportunity to enroll.
My prescriber has answered all my questions about Accutane and I understand that it is my responsibility not to get pregnant during Accutane treatment or for 1 month after I stop taking Accutane.
Initial:

I now authorize my prescriber _____ to begin my treatment with Accutane.
Patient Signature_____Date_____
Parent/Guardian Signature (if under age 18) _____Date_____
Patient Name (print)_____
Patient Address_____Telephone (___) _____
_____
I have:
• fully explained to the patient,_____ , the nature and purpose of Accutane treatment, including its benefits and risks
• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane
• answered those questions to the best of my ability
• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.
Prescriber Signature_____Date_____
Issued: November 2002

Patient Copy
18-013D-101-008-1102

((NCR FORM [2-part/part 1]))

Patient Qualification Form
for Pregnancy Prevention and
Contraception Compliance

((PPP Logo))

To be completed by the patient

Accutane (isotretinoin) is a very powerful medicine with the potential for serious Adverse Events. It is used to treat severe nodular acne that did not get better with other treatments, including oral antibiotics. Accutane can cause severe birth defects to your unborn baby if you use it while you are

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pregnant. It is contraindicated in females of childbearing potential unless your prescriber can qualify you with the following statements.

Patient qualification checklist

1. I am required to have 2 negative pregnancy tests showing that I am not pregnant before my prescriber can prescribe Accutane. I agree to schedule regular monthly appointments throughout my therapy for pregnancy tests and for other tests to monitor my body's response to Accutane. It is important to my health and well-being to keep every scheduled appointment faithfully. 1. [ ] YES [ ] NO

2. I am aware of the effects that Accutane may have on my unborn baby if I become pregnant during treatment and for 1 month following treatment. I have selected as my:
primary contraception method_____
and
secondary contraception method_____.
I will use both of these methods at the same time while on therapy and for 1 month afterward. 2. [ ] YES [ ] NO

3. My prescriber has given both oral and written warnings of the hazards of taking Accutane during pregnancy (exposing the fetus to the drug), and I have signed the Patient Information/Consent Form. 3. [ ] YES [ ] NO

4. I have been given the opportunity to participate in the Accutane Survey. 4. [ ] YES [ ] NO

_____
Patient's Name (print)

Patient's Signature Date

Prescriber Copy
18-013E-101-008-1102

((NCR FORM [2-part/part 1]))

Patient Qualification Form
for Pregnancy Prevention and
Contraception Compliance

((PPP Logo))

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To be completed by the patient

Accutane (isotretinoin) is a very powerful medicine with the potential for serious Adverse Events. It is used to treat severe nodular acne that did not get better with other treatments, including oral antibiotics. Accutane can cause severe birth defects to your unborn baby if you use it while you are pregnant. It is contraindicated in females of childbearing potential unless your prescriber can qualify you with the following statements.

Patient qualification checklist

1. I am required to have 2 negative pregnancy tests showing that I am not pregnant before my prescriber can prescribe Accutane. I agree to schedule regular monthly appointments throughout my therapy for pregnancy tests and for other tests to monitor my body's response to Accutane. It is important to my health and well-being to keep every scheduled appointment faithfully. 1. [ ] YES [ ] NO

2. I am aware of the effects that Accutane may have on my unborn baby if I become pregnant during treatment and for 1 month following treatment. I have selected as my:
primary contraception method_____
and
secondary contraception method_____.
I will use both of these methods at the same time while on therapy and for 1 month afterward. 2. [ ] YES [ ] NO

3. My prescriber has given both oral and written warnings of the hazards of taking Accutane during pregnancy (exposing the fetus to the drug), and I have signed the Patient Information/Consent Form.
3. [ ] YES [ ] NO

4. I have been given the opportunity to participate in the Accutane Survey. 4. [ ] YES [ ] NO

_____
Patient's Name (print)

_____
Patient's Signature Date

Patient Copy
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THIS SECTION CONTAINS MORE
INFORMATION FOR YOU

PLEASE READ THIS SECTION AND REVIEW
THESE DOCUMENTS AS OFTEN AS YOU NEED

((TAB Copy))
section 3
EDUCATION REINFORCEMENT

Preventing Pregnancy
A Guide to Contraception

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

Complete the Contraception Knowledge self-assessment located in the back of this booklet

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Introduction

Why is this information very important to me?

Your dermatologist may prescribe Accutane 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 systemic 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. 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 2 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 1 month after you completely stop taking Accutane. The section called Your sexual partner is provided to help you as you talk to your sexual

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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.

My role

What must I do before I can begin to take Accutane?
You must receive both oral and written warnings of the hazards of taking Accutane (isotretinoin) 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 2 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 5 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 1 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 pak. 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.

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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.

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 1 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.
Watch the video Be Aware: The Risk of Pregnancy While on Accutane (available from your prescriber).

((Illustrations of deformed babies))
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 all the severe internal defects that may occur, including those of the brain, heart, glands, and nervous system.

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Contraception Counseling Referral Program

Be sure to ask your prescriber about the Contraception Counseling Referral Program

Before you can start taking Accutane (isotretinoin), 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 healthcare professional will provide you with expert counseling about birth control.

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 that they may do. Be sure to ask your prescriber about the Contraception Counseling Referral Program.

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.

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• 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.
• MYTH (not true): I cannot become pregnant if I have ovary or womb disease (women's problems).
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 1 pill.
• MYTH (not true): I cannot get pregnant using fertility awareness or natural family planning if I have regular periods (or by having sex only during certain times of the month).
FACT: There is no "safe time" during your cycle 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 (isotretinoin)?

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

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

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you are not pregnant before, or become pregnant while you are taking Accutane or for 1 month after. In a survey conducted in women in the US, it was reported that approximately 50% of their pregnancies were unintended. 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.

Contraception methods[1]
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.

((Boxed Copy))
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.
((End Boxed Copy))

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 eggs from being released. 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 (isotretinoin) use.

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With the Pill method of birth control, 1 pill is taken once a day until the package is completed. The Pill is usually started the first Sunday after a normal menstrual period or as instructed by your healthcare professional. One package is completed every menstrual cycle. Not all pills provide protection from the start; you can become pregnant during the first 4 weeks 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 one 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.

Contraception methods

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 eggs from being released 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 only 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

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For current labeling information, please visit https://www.fda.gov/drugsatfda

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 eggs from being released, 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 2-3 women in 1000 become pregnant.
For typical use, the rate is also 2-3 in 1000.

Injectable hormones can take up to 1 week to be fully effective; you can become pregnant during this week. 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.

Contraception methods

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 one 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.

HORMONAL VAGINAL CONTRACEPTIVE RING

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((Illustrations of "ring" insertion))

This method of birth control is inserted by you into your vagina and contains a combination of hormones similar to the Pill. After the ring is inserted, it releases a continuous low dose of hormones into your body. The hormones stop the release of an egg and alter cervical mucus to keep sperm from entering the womb. You leave it in for 3 weeks, and then you remove it for 1 week. During this time, your menstrual period will begin. For your first cycle, the ring should be inserted between day 1 and day 5 of your menstrual period. It may take up to 1 week to become fully effective in the first cycle.

Generally, the side effects are similar to those of the Pill. Other side effects may include vaginal discharge or irritation. Like the Pill, the hormonal vaginal contraceptive ring may increase the risk of blood clots, heart attack, and stroke, especially in women who smoke. It should not be used by women with certain types of cancer or other medical conditions, so it is important to discuss these issues with your prescriber.

With perfect use, about 7-8 women in 1000 become pregnant.
For typical use, the rate is 1-2 in 100.

Remember: If the hormonal vaginal ring is your primary method, you must still use a secondary method at the same time. You cannot use the diaphragm as a secondary method because the vaginal contraceptive ring may interfere with correct placement and position of a diaphragm.

TRANSDERMAL HORMONAL PATCH

This method of birth control is delivered by a patch that you wear on your body and contains a combination of hormones similar to the Pill. After the patch is applied, its hormones are continuously transferred through your skin into your blood stream. The hormones prevent the release of an egg, alter vaginal mucous to keep the sperm from entering the womb, and keep a fertilized egg from attaching to the womb.

The patch should be applied once a week on the same day each week. During week 4, do not wear a patch. You should get your period during this week. Following week 4, repeat the same application routine every month.

The patch can be started either during the first 24 hours of your menstrual period, or on the first Sunday after your menstrual period begins. The patch may take up to one week to become fully effective. The patch can be applied on your buttock, abdomen, upper body (except breasts), or on the outside of your upper arm.

Generally, the side effects are similar to those of the Pill. The most common side effects include breast symptoms, headache, skin irritation at the application site, nausea, upper respiratory illness, menstrual cramps, and abdominal cramps. Like the Pill, the hormonal transdermal patch may increase the risk of blood clots, heart attack, and stroke, especially in women who smoke. It should not be used by women with certain types of cancer or other medical conditions, so it is important to discuss these issues with your prescriber.

If the patch falls off or is partially detached for less than 24 hours, try to reapply it to the same place or replace with a new patch immediately. This patch should be changed on the usual change day. If the

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patch is detached for more than 1 day, apply a new patch and begin a new 4-week cycle with a new Patch Change Day. This new patch will not be effective for contraception for the first week.

With perfect use, about 1 woman in 100 become pregnant.
For typical use, the rate is unknown.

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

Contraception methods

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 2 sperm 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.

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 (isotretinoin) 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, only count as ONE of the 2 effective methods of birth control you

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must choose before starting Accutane. The diaphragm or cervical cap must be left in place for 6 hours after your last sexual act, 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 earlier.

Contraception methods

((Illustration of condom use))
CONDOM

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. It is also believed that latex condoms reduce the spread of some 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. However, since it is necessary to use a spermicide with a condom, this can be used as a lubricant. 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.
((Illustrations of diaphragm use))

Contraception methods

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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.
((Illustrations of cervical cap use))

Other contraception methods

Do not use less effective methods of birth control such as birth control pills without estrogen, natural family planning, (having sex only certain times of the month) fertility awareness, or withdrawal while taking Accutane (isotretinoin), 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.

Reference: 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.

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Pregnancy and pregnancy testing

Early signs of pregnancy

While you are taking Accutane (isotretinoin), you want to be sure that you are not pregnant or do not become pregnant. That is the reason you are using 2 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. If you think you might be 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.
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

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• Irregular bleeding or spotting with abdominal pain when your period is late
• Fainting or dizziness lasting more than a few seconds

Testing for Pregnancy
If you have any questions about whether or not you are pregnant, please speak to your prescriber or contraception counselor. There are many urine pregnancy tests available. Please review and follow specific test instructions on the kit you choose to use.

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 2 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

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 (isotretinoin), 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 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

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• 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

((Image of videocassette))

The Accutane Survey

Lots of other women who have taken Accutane have participated in the 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 they were worried about privacy, thought the Survey might be too much paperwork, or were afraid that it might be like taking a test.

Please do not worry: The Survey is absolutely confidential. Only the researchers at SI International 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.

((Image of Accutane Survey form))

Confidential Contraception Counseling Line

The Confidential Contraception Counseling Line phone number is 1-800-542-6900.
The Confidential Contraception Counseling Line is a 24-hour toll-free line available to all patients on Accutane (isotretinoin). You can call this line as many times as you want, and at any time of day, to receive confidential information on Accutane, birth defects, sex and birth control, contraception, pregnancy and pregnancy prevention, emergency contraception, and the Accutane Survey. Share this

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information and the phone number with members of your family and your partner. Remember, it is completely confidential, you will never have to give your name, and you cannot be identified.

Telephone Menu: After the introduction, listen to the following menu and press the corresponding number on your telephone keypad to learn more about:

Birth Defects/Teratogenicity — Press 1
Press 1. What does teratogenicity mean?
Press 2. How can you avoid birth defects?
Press 3. When do you have to worry about teratogenicity while using Accutane?
Press 4. How long do I have to wait after taking Accutane to become pregnant?
Press 5. What should I do if I think I may be pregnant?

Sex and Birth Control — Press 2
Press 1. What is abstinence?
Press 2. What is unprotected sex?
Press 3. Are you unsure whether or not you can get pregnant?
Press 4. Why do I need to know if I might have sex in the near future?
Press 5. Why do I need to know about the birth control I use?
Press 6. Myths about pregnancy and contraception

Contraceptive Methods/Birth Control — Press 3
Press 1. What does 2 forms of birth control mean?
Press 2. How do I use 2 in combination?
Press 3. Questions about specific methods of birth control
- Press 1. Abstinence
- Press 2. The Pill
- Press 3. Implantable hormones
- Press 4. Injectable hormones
- Press 5. Intrauterine device
- Press 6. Sterilization
- Press 7. Condom
- Press 8. Diaphragm
- Press 9. Cervical cap
- Press 10. Spermicide
- Press 11. Withdrawal
- Press 12. Fertility awareness methods

Press 4. What if I forget my birth control or if my birth control fails?

Information on Emergency Contraception — Press 4
Press 1. What should you do if you think you may be pregnant?
Press 2. Questions about emergency contraception
Press 3. Possible effects on the fetus/baby if you get pregnant while on Accutane
Press 4. What should you do if you think you may be pregnant?

Pregnancy and Pregnancy Testing — Press 5

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Press 1. What should you do if you think you may be pregnant?
Press 2. Pregnancy tests
    Press 1. When do I perform a pregnancy test?
    Press 2. What is the difference between a blood and urine test?
    Press 3. Where can I get a pregnancy test?
    Press 4. What if I have my period? Can I take a test if I do?
Press 3. Myths about pregnancy and contraception

The Accutane Survey — Press 6
Press 1. Why should I join?
Press 2. How do I join?
Press 3. What is the benefit to me?
Press 4. Is it confidential?

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

Accutane InfoLine
((PPP Logo))

ENGLISH
The Accutane InfoLine gives you information on Accutane. To call, dial toll-free 1-800-950-4411 on a touchtone phone. When you hear the three tones, push "1" to hear the message in English. You will hear the facts about Accutane, but you may not hear all there is to know about Accutane. Be sure to ask your doctor for complete information. Please call…we'd like to share important facts with patients taking Accutane.
((Also translated into Spanish, Portuguese, Italian, French, Russian, German, Polish, Vietnamese, Korean, Japanese, and Chinese))

Scenes from the video
If you are taking Accutane, it can be harmful to your unborn baby. It's important for you to know how to avoid pregnancy

((PPP Logo))

Please take the time to watch the 4-minute video, Be Prepared, Be Protected

"I guess I didn't know…now I do."
It's important to know what abstinence means. That means not having sex. Not once, not twice, not ever.

"It was just one
time…this can't be right."

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If you are having sex at any time you can't use any excuses. It doesn't matter if your periods are irregular or if you think you can't get pregnant or if you don't have sex frequently. Once can be enough.

"But this time,
I guess it…it didn't work."
Withdrawal is not reliable.
You must use effective birth control, such as the contraceptive pill, diaphragm or condom. And if you are taking a medication that may cause birth defects to your unborn baby, you must use 2 separate, effective methods of birth control at the same time.

"I didn't think this would happen…"
You have to think about birth control beforehand. Don't be caught unprepared. You may have sex, and you might become pregnant. Don't assume your partner will take responsibility.

"What if I get pregnant?…What am I going to do?"
Always make sure your birth control is reliable and effective. If you have any questions about it, or about your medical treatment, ask your prescriber or nurse.

Summary

If you want to be treated with Accutane (isotretinoin), 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 1 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 5 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 1 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.

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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 1 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 1 primary form of birth control and 1 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 Be Smart, Be Safe, Be Sure booklet under Section 3, Preventing Pregnancy—A Guide to Contraception, and then speak to your prescriber

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

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5. If your 2 birth control methods are the Pill and the diaphragm, and you forgot to take 2 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 2 at a time until you catch up

6. The reason you are being asked to use 2 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 and 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

((Roche Logo))

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Be Smart Be Safe Be Sure™
Accutane® (isotretinoin)
Risk Management
Program for Men

If you have any questions about your therapy, please contact:
Name:_____
(to be completed by Prescriber)

Telephone: _____

Complete the three sections in this order:
Section 1
Education — Review this material before completing the consent form
• Reproduction information for men
• Patient Product Information, Important information concerning your treatment with Accutane® (isotretinoin)

Section 2
Consent — Complete this section with your prescriber
• Informed Consent/Patient Agreement form

Section 3
Education Reinforcement
• Accutane InfoLine

IMPORTANT INFORMATION TO READ
BEFORE YOU RECEIVE YOUR
ACCUTANE® (isotretinoin) PRESCRIPTION

((TAB Copy))
section 1
EDUCATION

Reproduction information for men

Booklets and packages for Accutane® (isotretinoin) 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?

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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 defects 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 a greatly increased amount of isotretinoin circulating in their blood. For this reason, neither males nor females should donate blood while taking Accutane or for 1 month after stopping Accutane, as the blood levels may be high enough to cause birth defects if the blood is given to 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, Important Information Concerning Your Treatment with Accutane® (isotretinoin) following this page begins with information for women. If isotretinoin is taken during pregnancy, the unborn babies may have terrible birth defects.
These birth defects may have been avoided if the mother had not been taking isotretinoin while she was pregnant. Male patients should note that the Patient Product Information 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 System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™). The program 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 the pharmacist knows patients have been approved 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.

((Qualification Sticker art))

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

((Boxed Copy))
To summarize:

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• Never share Accutane with anyone else.
• Do not donate blood during your Accutane treatment or for 1 month after stopping Accutane, to give the drug time to leave the bloodstream.
((End Boxed Copy))

For more information, please read the Patient Product Information and the Medication Guide.

Ninth Edition
November 2002

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.

Things you should know about

Accutane (isotretinoin) 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 read this brochure carefully and ask your prescriber any questions you may have.

Possible serious side effects of Accutane include birth defects and mental disorders.
IMPORTANT INFORMATION FOR FEMALE PATIENTS:
BIRTH DEFECTS (Causes Birth Defects)

((Boxed Copy))
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).

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You will not get your first prescription for Accutane until there is proof that 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 5 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 30-day 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 topical/injectable (shots)/implantable/insertable hormonal birth control 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, 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.
((End Boxed Copy))

((Boxed Copy))
((Image of deformed babies))
((End Boxed Copy))

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 all the severe internal defects that may occur, including those of the brain, heart, glands, and nervous system.

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, 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

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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, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- Have a change in your appetite or body weight
- Have trouble concentrating
- Withdraw from your friends or family
- Feel like you have no energy
- Have feelings of worthlessness or inappropriate guilt
- Start having thoughts about hurting yourself or taking your own life (suicidal thoughts)

What is Accutane?
Accutane is used to treat the most severe form of acne (nodular acne)
that 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 figures). 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.

((Images of skin cross-sections))

General guidelines for taking your medication

Who should not take Accutane?

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Do not take Accutane (isotretinoin) if you are pregnant, plan to become pregnant, or become pregnant during Accutane treatment. Accutane causes severe birth defects. Please carefully read "Important Information for Female Patients: Birth Defects" on page 1.2.

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, osteoporosis (bone loss), weak bones, anorexia nervosa (an eating disorder where people eat too little), 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 a 30-day 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 a yellow sticker.
- The amount of Accutane you take has been specially chosen for you and may change during your 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. Swallow your Accutane capsules with a full glass of liquid. This will help prevent the medication inside the capsule from irritating the lining of your esophagus (connection between mouth and stomach). For the same reason, do not chew or suck on the capsule.
- If you miss a dose, just skip that dose. Do not take 2 doses 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?
- Do not get pregnant while taking Accutane and for 1 month after stopping 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 light. Accutane may make your skin more sensitive to light.

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Important information for all patients

- 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 prescriber 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.
- Talk with your prescriber if you are currently taking an oral or injected corticosteroid or anticonvulsant (seizure) medication prior to using Accutane. These drugs may weaken your bones.
- Do not share Accutane with other people. It can cause birth defects and other serious health problems.
- Do not take Accutane with antibiotics unless you talk to your prescriber. For some antibiotics, you may have to stop taking Accutane until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain.

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 mothers took Accutane while they were pregnant. Please read "Important Information for Female Patients: Birth Defects" on page 1.2.
- Serious mental health problems. Please see "Mental disorders and suicide" on page 1.3.
- Serious brain problems. Accutane can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Accutane and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking Accutane have had seizures (convulsions) or stroke.
- Abdomen (stomach area) problems. Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Accutane. Stop taking Accutane and call your prescriber if you get severe stomach, chest or bowel pain; have trouble swallowing or painful swallowing; get new or worsening heartburn, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine.
- Bone and muscle problems. Accutane may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your prescriber if you plan vigorous physical activity during treatment with Accutane. Tell your prescriber if you develop pain, particularly back pain or joint pain. There are reports that some patients have had stunted growth after taking Accutane for acne as directed. There are also some reports of broken bones or reduced healing of broken bones after taking Accutane for acne as directed. No one knows if taking Accutane for acne will affect your bones. If you have a broken bone, tell your prescriber that you are taking Accutane. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens, stop taking Accutane, and call your prescriber right away.
- Hearing problems. Some people taking Accutane have developed hearing problems. It is possible that hearing loss can be permanent. Stop using Accutane and call your prescriber if your hearing gets worse or if you have ringing in your ears.

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• 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 when 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.

After your treatment is completed
• Lipid (fats and cholesterol in blood) problems. Many people taking Accutane (isotretinoin) 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.

After your treatment is completed

For female patients:
• You must continue using 2 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.

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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 1 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 leftover Accutane to anyone. It can cause birth defects and other serious health problems.

PLEASE COMPLETE THIS SECTION WITH
YOUR PRESCRIBER OR NURSE

((TAB Copy))
SECTION 2
CONSENT

((NCR FORM))
ACCUTANE® (isotretinoin)
Informed Consent/PATIENT AGREEMENT
(for all patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

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

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

1. I, _____,
(Patient's Name)
understand that Accutane is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.
Initials: _____
2. My prescriber has told me about my choices for treating my acne.
Initials: _____
3. I understand that there are serious side effects that may happen while I am taking Accutane. These have been explained to me. These side effects include serious birth defects in babies of pregnant females. (Note: There is a second Informed Consent form for female patients concerning birth defects.)
Initials: _____
4. I understand that some patients, while taking Accutane or soon after stopping Accutane, have become depressed or developed other serious mental problems. Symptoms of these problems include

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

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), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

Initials: _____

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

Initials: _____

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

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Patient Signature_____Date_____

Parent/Guardian Signature (if under age 18)_____Date_____

Patient Name (print)_____

Patient Address_____Telephone (_____) _____

_____

I have:

• fully explained to the patient,_____, the nature and purpose of Accutane treatment, including its benefits and risks

• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane

• answered those questions to the best of my ability

• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.

Prescriber Signature_____Date_____

Issued: November 2002

Prescriber Copy
18-013-101-009-1102

((NCR FORM))
ACCUTANE® (isotretinoin)
Informed Consent/PATIENT AGREEMENT
(for all patients)
To be completed by patient (parent or guardian if patient is under age 18) and signed by the prescriber

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

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

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

Initials: _____

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

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Initials: _____

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

Initials: _____

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

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), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

Initials: _____

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

Initials: _____

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

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Initials: _____

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

Patient Signature_____Date_____

Parent/Guardian Signature (if under age 18)_____Date_____

Patient Name (print)_____

Patient Address_____Telephone (_____) _____

_____

I have:

• fully explained to the patient,_____, the nature and purpose of Accutane treatment, including its benefits and risks

• given the patient the appropriate educational materials, Be Smart, Be Safe, Be Sure, for Accutane and asked the patient if he/she has any questions regarding his/her treatment with Accutane

• answered those questions to the best of my ability

• placed the yellow self-adhesive Accutane Qualification Sticker on the prescription.

Prescriber Signature_____Date_____

Issued: November 2002

Patient Copy

18-013-101-009-1102

THIS SECTION CONTAINS MORE INFORMATION FOR YOU

((TAB Copy))

section 3

EDUCATION REINFORCEMENT

Accutane InfoLine

ENGLISH

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NDA 18-882/S048/S052

The Accutane (isotretinoin) InfoLine gives you information on Accutane. To call, dial toll-free 1-800-950-4411 on a touchtone phone. When you hear the three tones, push "1" to hear the message in English. You will hear the facts about Accutane, but you may not hear all there is to know about Accutane. Be sure to ask your doctor for complete information. Please call…we'd like to share important facts with patients taking Accutane.
((Also translated into Spanish, Portuguese, Italian, French, Russian, German, Polish, Vietnamese, Korean, Japanese, and Chinese))

((Roche Signoff))
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ACCUTANE® QUALIFICATION STICKER

_____ Female _____ Male

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

Qualification date

QSXXXXXXXX DEA # ABXXXXXXX

Pharmacist:

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

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