

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590  
(516) 222-6222 • FAX (516) 683-1887

4200 02 APR 16 A9:12

April 15, 2002

**OVERNIGHT COURIER 4/15/02**

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**CITIZEN PETITION**

This petition is submitted in quadruplicate pursuant to 21 CFR 314.93, and Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of Food and Drug Administration to declare that the drug product, Isotretinoin Capsules 30 mg, is suitable for submission as an abbreviated new drug application (ANDA).

**A. Action Requested**

The petitioner requests that Commissioner of the Food and Drug Administration declare that Isotretinoin Capsules USP, 30 mg is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is Accutane® (Isotretinoin) Capsules, 40 mg. The petitioner also references Accutane Capsules, 10 mg and 20 mg in support of this petition. Accutane® has been approved as safe and effective by the FDA, and its listing appears on pages 3-206 and 3-207 of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) 21<sup>st</sup> Edition (Attachment A). The petitioner seeks only a change in strength from that of the reference listed drug product to include a 30 mg intermediate strength capsule.

**B. Statement of Grounds**

Accutane® Capsules, the reference-listed drug upon which this petition is based, is available in dosage strengths of 10 mg, 20 mg, and 40 mg capsules. The labeling of the reference-listed drug provides for a dosage range of 0.5 to 1 mg / kg and recommends the total daily dose be administered in two divided doses. The addition of a 30 mg strength of Isotretinoin Capsules will provide the physician with the flexibility to select an appropriate dosage strength for the patients in a weight range where the most appropriate dosage is best delivered in multiples of 30 mg. Providing a 30 mg dose in a single capsule will also provide for greater convenience for the patient, as only one capsule instead of two will need to be taken to obtain the desired dose.

02P-0161

CP 1

There should be no questions of safety or efficacy raised regarding the requested change in strength, as the proposed strength represents an intermediate strength between two already safe and effective doses. In addition, a 30 mg strength product is clearly defined and contemplated in the approved labeling of the reference-listed drug product for a readily identifiable patient population by the mg / kg dosage recommendations.

Labeling of the proposed product (Attachment B) will be the same as the approved labeling of reference-listed drug product (Attachment C) with exception of the introduction of the 30 mg strength in the "Description" and "How supplied" sections of the labeling. The dosing recommendations will remain unaltered, as the approved labeling already covers the provision for 30 mg strength based on mg / kg basis. In addition, the petitioner acknowledges that it will comply with the Agency's requirement to establish a program similar to the S.M.A.R.T. Program of Roche as a part of the complete labeling.

**C. NOT REQUIRED TO ADDRESS THIS ISSUE FOR A CHANGE IN STRENGTH**

**D. Environmental Impact**

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.31(a).

**E. Economic Impact**

This information will be provided upon request by the Agency.

**F. Certification**

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which is unfavorable to the petition.

Sincerely,



Robert W. Pollock  
Vice President  
Lachman Consultant Services, Inc.  
1600 Stewart Avenue  
Westbury, NY 11590

cc: Gregg Davis, OGD

RAP2098b

**ATTACHMENT A**

PRESCRIPTION DRUG PRODUCT LIST

3-206

ISOSORBIDE DINITRATE

TABLET; SUBLINGUAL  
ISOSORBIDE DINITRATE  
AB GENEVA PHARMS 2.5MG  
AB 5MG  
AB WEST WARD 2.5MG  
AB 5MG

TABLET, CHEWABLE; ORAL  
 SORBITRATE  
 ASTRAZENACA 5MG  
 + 10MG

TABLET, EXTENDED RELEASE; ORAL  
 ISOSORBIDE DINITRATE  
 + INWOOD LABS 40MG

ISOSORBIDE MONONITRATE

TABLET; ORAL  
ISMO  
AB ROBINS AH 20MG  
AB ISOSORBIDE MONONITRATE  
 PUREPAC PHARM 10MG  
AB 20MG  
AB TEVA 20MG  
AB WEST WARD 20MG  
AB MONOKET  
 SCHWARZ 10MG  
AB + 20MG

TABLET, EXTENDED RELEASE; ORAL  
IMDUR  
AB + SCHERING 30MG

ISOSORBIDE MONONITRATE

TABLET, EXTENDED RELEASE; ORAL  
IMDUR  
AB + SCHERING 60MG  
AB + 120MG  
AB ISOSORBIDE MONONITRATE  
 BRIGHTSTONE 60MG  
AB DEXCEL LTD 60MG

AB ELAN PHARM 60MG  
AB KREMERS URBAN 30MG  
AB 60MG  
AB 120MG  
AB KV PHARM 30MG  
AB 60MG  
AB 120MG  
AB PUREPAC PHARM 30MG  
AB 60MG  
AB ZENITH GOLDLINE 60MG

N86225 001  
 FEB 19, 1988  
N86222 001  
 FEB 19, 1988  
N86054 001  
 OCT 29, 1987  
N86055 001  
 NOV 02, 1987  
N16776 002  
 APR 01, 1996  
N16776 003  
 APR 01, 1996  
N40009 001  
 DEC 30, 1998  
N19091 001  
 DEC 30, 1991  
N75037 002  
 OCT 30, 1998  
N75037 001  
 OCT 30, 1998  
N75147 001  
 NOV 27, 1998  
N75361 001  
 OCT 05, 2000

N20215 002  
 JUN 30, 1993  
N20215 001  
 JUN 30, 1993

N20225 001  
 AUG 12, 1993

ISOSULFAN BLUE

INJECTABLE; INJECTION  
 LYMPHAZURIN  
 + US SURGCL 1 $\frac{1}{2}$

ISOTRETINOIN

CAPSULE; ORAL  
 ACCUTANE  
 HLR. 10MG

N20225 002  
 AUG 12, 1993  
N20225 003  
 MAR 30, 1995

N75166 001  
 OCT 07, 1999  
N75522 001  
 APR 17, 2000  
N75041 001  
 SEP 22, 1998  
N75155 002  
 JAN 13, 2000  
N75155 001  
 OCT 30, 1998  
N75155 003  
 AUG 04, 2000  
N75395 001  
 MAR 16, 2000  
N75395 002  
 MAR 16, 2000  
N75395 003  
 MAR 16, 2000  
N75306 001  
 DEC 31, 1998  
N75306 002  
 DEC 31, 1998  
N75448 001  
 JUN 19, 2000

N18310 001

N18662 002  
 MAY 07, 1982

PRESCRIPTION DRUG PRODUCT LIST

3-207

ISOTRETINOIN

CAPSULE; ORAL  
ACCUTANE  
HLR 20MG N18662 004  
MAR 28, 1983  
+ 40MG N18662 003  
MAY 07, 1982

ISRADIPINE

CAPSULE; ORAL  
DYNACIRC  
NOVARTIS 2.5MG N19546 001  
DEC 20, 1990  
+ 5MG N19546 002  
DEC 20, 1990

TABLET, EXTENDED RELEASE; ORAL  
DYNACIRC CR 5MG N20336 001  
+ NOVARTIS JUN 01, 1994  
+ 10MG N20336 002  
JUN 01, 1994

ITRACONAZOLE

CAPSULE; ORAL  
SPORANOX  
+ JANSSEN 100MG N20083 001  
SEP 11, 1992

INJECTABLE; INJECTION  
SPORANOX  
+ JANSSEN 10MG/ML N20966 001  
MAR 30, 1999

SOLUTION; ORAL  
SPORANOX  
+ JANSSEN 10MG/ML N20657 001  
FEB 21, 1997

IVERMECTIN

TABLET; ORAL  
STROMEKTOL  
MERCK 3MG N50742 002  
+ 6MG N50742 001  
OCT 08, 1998  
NOV 22, 1996

KANAMYCIN SULFATE

CAPSULE; ORAL  
KANTREX  
+ APOTHECON EQ 500MG BASE N62726 001  
MAR 06, 1987

INJECTABLE; INJECTION

KANAMYCIN SULFATE  
LOCH EQ 1GM BASE/3ML N63025 001  
JUL 31, 1992  
AP EQ 75MG BASE/2ML N63021 001  
JUL 31, 1992  
AP EQ 500MG BASE/2ML N63022 001  
JUL 31, 1992  
AP STERIS EQ 1GM BASE/3ML N62520 003  
MAY 09, 1985

KANTREX  
AP + APOTHECON EQ 75MG BASE/2ML N61901 003  
AP + EQ 500MG BASE/2ML N61901 001  
AP + EQ 1GM BASE/3ML N61901 002

KETAMINE HYDROCHLORIDE

INJECTABLE; INJECTION  
KETALAR  
AP + PARKEDALE EQ 50MG BASE/ML N16812 002  
AP + EQ 100MG BASE/ML N16812 003  
+ EQ 10MG BASE/ML N16812 001

KETAMINE HCL  
AP ABBOTT EQ 50MG BASE/ML N74549 001  
JUN 27, 1996  
AP EQ 100MG BASE/ML N74549 002  
JUN 27, 1996  
AP BEDFORD EQ 50MG BASE/ML N74524 001  
MAR 22, 1996  
AP EQ 100MG BASE/ML N74524 002  
MAR 22, 1996

**ATTACHMENT B**

## ISOTRETINOIN CAPSULES USP

Rx only

### CAUSES BIRTH DEFECTS



### AVOID PREGNANCY

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

Major human fetal abnormalities related to isotretinoin capsules 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.

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

Isotretinoin must be prescribed under the *System for Prevention of Isotretinoin Related Teratogenicity (S.P.I.R.T.)*

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

- 1) Read the booklet entitled *System for Prevention of Isotretinoin Related Teratogenicity (S.P.I.R.T.) Guide to Best Practices*
- 2) Sign and return the completed S.P.I.R.T. *Letter of Understanding* containing the following Prescriber Checklist:
  - I know the risk and severity of fetal injury/birth defects from Isotretinoin
  - 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 Isotretinoin therapy and for 1 month after stopping Isotretinoin. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Isotretinoin 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 Isotretinoin treatment course, the S.P.I.R.T. procedures for Isotretinoin, including monthly pregnancy avoidance counseling, pregnancy testing and use of Isotretinoin Qualification Stickers
- 3) To use the yellow self-adhesive Isotretinoin Qualification Sticker: Isotretinoin should not be prescribed or dispensed to any patient (male or female) without a yellow self-adhesive Isotretinoin Qualification Sticker.

For female patients, the yellow self-adhesive Isotretinoin 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 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 Isotretinoin. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Isotretinoin therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated every month prior to the female patient receiving each prescription. The manufacturer will make available urine pregnancy test kits for female Isotretinoin patients for the initial, second and monthly testing during therapy.
- **Must** have selected and has 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 Isotretinoin therapy, during Isotretinoin therapy, and for 1 month after discontinuing Isotretinoin therapy. Counseling about contraception and

behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

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

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Isotretinoin. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports occurred while these patients were taking isotretinoin capsules. 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 Isotretinoin Survey and has been given the opportunity to enroll (see PRECAUTIONS).

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

If a pregnancy does occur during treatment of a woman with Isotretinoin, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to the manufacturer @ 1-800-XXX-XXXX where a Pregnancy Avoidance Program Specialist (PAP) will be available to discuss pregnancy information, or prescribers

may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

Isotretinoin 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.P.I.R.T. *Guide to Best Practices*, signed and returned the completed S.P.I.R.T. *Letter of Understanding*, and obtained yellow self-adhesive Isotretinoin Qualification Stickers. Isotretinoin should not be prescribed or dispensed without a yellow self-adhesive Isotretinoin Qualification Sticker.

**INFORMATION FOR PHARMACISTS:**

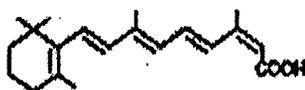
**ISOTRETINOIN MUST ONLY BE DISPENSED:**

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

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

**DESCRIPTION:** Isotretinoin, a retinoid, is available as Isotretinoin in 10-mg, 20-mg, 30-mg and 40-mg soft gelatin capsules for oral administration. Each capsule contains butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil, hydrogenated vegetable oil iron oxide black, soybean oil and white wax. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 30 mg — FD&C Yellow No. 6 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-orange 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 patients with nodular acne 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 Isotretinoin, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.<sup>1</sup>

**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 dose (2 x 40 mg capsules) of isotretinoin under fasted and fed conditions. Both peak plasma concentration ( $C_{max}$ ) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with isotretinoin given under fasted conditions (see Table 1 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, Isotretinoin 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 1. Pharmacokinetic Parameters of Isotretinoin**  
(Mean (%CV), N=74)

Isotretinoin 2 x 40 mg Capsules	AUC 0-∞ (ng.hr/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (hr)	$T_{1/2}$ (hr)
Fed	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

**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*-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 isotretinoin 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. After multiple oral dose administration of isotretinoin to adult cystic acne patients ( $\geq$  18 years), the exposure to patients to 4-*oxo*-isotretinoin at steady state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin. Given its abundance and degree of retinoid activity, it is most likely that 4-*oxo*-isotretinoin is a significant contributor to the activity 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 excreted in urine and feces.

**Elimination:** Following oral administration of an 80 mg dose of  $^{14}\text{C}$ -isotretinoin as a liquid suspension,  $^{14}\text{C}$ -activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg oral dose of isotretinoin to 74 healthy adult subjects under fed conditions, the mean  $\pm$  SD elimination half-lives ( $t_{1/2}$ ) of isotretinoin and 4-*oxo*-isotretinoin were  $21.0 \pm 8.2$  hours and  $24.0 \pm 5.3$  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.

**INDICATIONS AND USAGE:** *Severe Recalcitrant Nodular Acne:* Isotretinoin 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,<sup>2</sup> means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Isotretinoin should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Isotretinoin is indicated only for those females who are not pregnant, because Isotretinoin can cause severe birth defects (see boxed CONTRAINDICATIONS AND WARNINGS).

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

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

**Allergic Reactions:** Isotretinoin is contraindicated in patients who are hypersensitive to this medication or to any of its components. Isotretinoin 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:*** Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Isotretinoin 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 Isotretinoin".

***Pseudotumor Cerebri:*** Isotretinoin 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 Isotretinoin 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. Isotretinoin should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

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

Blood lipid determinations should be performed before Isotretinoin is given and then at intervals until the lipid response to Isotretinoin 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 Isotretinoin therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Isotretinoin 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 Isotretinoin are unknown. ***Animal Studies:*** In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 or 5.3 times the recommended clinical dose of 1.0 mg/kg/day after normalization of 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

*Decreased Night Vision:* Decreased night vision has been reported during isotretinoin 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 Isotretinoin Pregnancy Prevention Risk Management Program consists of the *System for Prevention of Isotretinoin Related Teratogenicity (S.P.I.R.T.)* and the *Isotretinoin Pregnancy Avoidance Program (PAP)*. S.P.I.R.T. should be followed for prescribing Isotretinoin with the goal of preventing fetal exposure to isotretinoin. It consists of: 1) reading the booklet entitled *System for Prevention of Isotretinoin Related Teratogenicity (S.P.I.R.T.) Guide to Best Practices*, 2) signing and returning the completed S.P.I.R.T. *Letter of Understanding* containing the Prescriber Checklist, 3) a yellow self-adhesive Isotretinoin Qualification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Isotretinoin Pregnancy Avoidance Program (PAP)* should be used with each patient.

The following further describes each component:

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

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

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

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

The booklet for male patients, Reproduction Information for Men also includes information about male reproduction, a warning not to share Isotretinoin with others or to donate blood during Isotretinoin therapy and for 1 month following discontinuation of Isotretinoin.

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

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

- Patients should be instructed to read the Medication Guide supplied as required by law when Isotretinoin 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 Isotretinoin*". All patients should sign the Informed Consent/Patient Agreement.
- Females of childbearing potential should be instructed that they must not be pregnant when Isotretinoin therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Isotretinoin, while taking Isotretinoin, and for 1 month after Isotretinoin has been stopped. They should also sign a consent form prior to beginning Isotretinoin therapy. They should be given an opportunity to enroll in the Isotretinoin Survey and to review the patient videotape provided by the manufacturer to the prescriber. It includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another Isotretinoin prescription is written (see boxed CONTRAINDICATIONS AND WARNINGS).
- Isotretinoin is found in the semen of male patients taking isotretinoin capsules, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of post marketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.

- 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 Isotretinoin therapy is appropriate in this setting. (see WARNINGS: *Psychiatric*).
- Patients should be informed that they must not share Isotretinoin with anyone else because of the risk of birth defects and other serious adverse events.
- Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Isotretinoin.
- Patients should be reminded to take Isotretinoin 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 Isotretinoin therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS: *Skin and Appendages*).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with isotretinoin capsules in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of isotretinoin capsules, but in some cases persisted (see ADVERSE REACTIONS: *Musculoskeletal*). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see Laboratory Tests: CPK).
- Neutropenia and rare cases of agranulocytosis have been reported. Isotretinoin 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 Isotretinoin to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- *Tetracyclines:* Concomitant treatment with Isotretinoin and tetracyclines should be avoided because isotretinoin 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 isotretinoin 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with isotretinoin. Therefore, it is critically important for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see boxed CONTRAINDICATIONS AND WARNINGS).
- *Phenytoin:* Isotretinoin 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.

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

### *Laboratory Tests:*

*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 Isotretinoin prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Isotretinoin, (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 Isotretinoin 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 Isotretinoin is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin 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 Isotretinoin has been established (see WARNINGS: *Hepatotoxicity*).
- *Glucose*: Some patients receiving isotretinoin capsules have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin therapy, although no causal relationship has been established.
- *CPK*: Some patients undergoing vigorous physical activity while on isotretinoin therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare post-marketing reports of rhabdomyolysis, some associated with strenuous physical activity.

*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 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 Isotretinoin.

**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 the elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see **WARNINGS AND PRECAUTIONS**)

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

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

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

**Cardiovascular:** palpitation, tachycardia, vascular thrombotic disease, stroke

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

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

*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 (see WARNINGS: *Skeletal*), mild to moderate musculoskeletal symptoms including 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 (see WARNINGS: *Psychiatric Disorders*), emotional instability

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

*Reproductive System:* abnormal menses

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

*Skin and Appendages:* acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas<sup>7</sup>, 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* 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<sub>50</sub> 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, overdose has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without apparent residual effects.

Isotretinoin causes serious birth defects at any dosage (see boxed CONTRAINDICATIONS AND WARNINGS.) Females with childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the boxed CONTRAINDICATIONS AND WARNINGS. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in the Boxed Warning. 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:** Isotretinoin should be administered with a meal (see PRECAUTIONS: *Information for Patients and Prescribers*).

The recommended dosage range for Isotretinoin is 0.5 to 1.0 mg/kg/day given in two divided doses for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,<sup>8</sup> 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. 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 Isotretinoin with food will significantly decrease absorption. Before upward dose adjustments are made, the patient should be questioned about their compliance with food instructions.

The safety of once daily dosing with Isotretinoin 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 (see WARNINGS: *Skeletal: Hyperostosis and Premature Epiphyseal Closure*).

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

**Table 3. Isotretinoin Dosing by Body Weight (Based on Administration With Food)**

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

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

**Information for Pharmacists:** Isotretinoin must only be dispensed in no more than a 1-month supply and only on presentation of a Isotretinoin prescription with a yellow self-adhesive Isotretinoin Qualification Sticker written within the previous 7 days. **REFILLS REQUIRE A NEW WRITTEN PRESCRIPTION WITH A YELLOW-SELF ADHESIVE ISOTRETINOIN QUALIFICATION STICKER WITHIN THE PREVIOUS 7 DAYS.** No telephone or computerized prescriptions are permitted.

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

**HOW SUPPLIED:** Soft gelatin capsules, 10 mg (light pink), imprinted "M10". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-666-80).

Soft gelatin capsules, 20 mg (maroon), imprinted "M20". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-667-80).

Soft gelatin capsules, 30 mg (golden yellow), imprinted "M30". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-447-80).

Soft gelatin capsules, 40 mg (yellow), imprinted "M40". Boxes of 100 containing 10 Prescription Packs of 10 capsules (NDC 63304-668-80).

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

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**ISOTRETINOIN 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 Isotretinoin if there is anything that you do not understand.**

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

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

Initial: \_\_\_\_\_

2. I understand that I must not take 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 Isotretinoin.

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

Initial: \_\_\_\_\_

6. I will talk with my prescriber about any drugs or herbal products I plan to take during my Isotretinoin 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, 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 kill sperm.

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

Initial: \_\_\_\_\_

8. I understand that I may receive a free contraceptive (birth control) counseling session and pregnancy testing from a doctor or other family planning expert. My Isotretinoin prescriber can give me a Isotretinoin 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 one month before I start taking Isotretinoin.

Initial: \_\_\_\_\_

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

Initial: \_\_\_\_\_

11. I understand that I should not start taking Isotretinoin 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 brochure *Important Information Concerning Your Treatment with Isotretinoin*. My prescriber gave me and asked me to watch the video about contraception. I was told about a confidential counseling line that I may call for more information about birth control. I have received information on emergency contraception (birth control).

Initial: \_\_\_\_\_

13. I understand that I must stop taking Isotretinoin 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 two birth control methods at any time.

Initial: \_\_\_\_\_

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

Initial: \_\_\_\_\_

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

- have had two negative urine or serum pregnancy tests before receiving the initial Isotretinoin 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 two forms of effective contraception simultaneously, at least one of which must be a primary form, unless absolute abstinence is the chosen method, or I have undergone a hysterectomy. I must use two forms of contraception for at least 1 month prior to initiation of Isotretinoin therapy, during therapy, and for 1 month after discontinuing therapy. I must receive counseling, repeated on a monthly basis, about contraception and behaviors associated with an increased risk of pregnancy.
- have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.

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

Initial: \_\_\_\_\_

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

I now authorize my prescriber \_\_\_\_\_ to begin my treatment with Isotretinoin

Patient signature: \_\_\_\_\_ Date: \_\_\_\_\_

Parent/guardian signature (if under age 18): \_\_\_\_\_ Date: \_\_\_\_\_

Please print: Patient name and address \_\_\_\_\_

\_\_\_\_\_ Telephone (area code) \_\_\_\_\_

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 Isotretinoin and have answered those questions to the best of my ability.

Prescriber signature: \_\_\_\_\_ Date: \_\_\_\_\_

**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 Isotretinoin if there is anything that you do not understand about all the information you have received about using Isotretinoin.**

1. I, \_\_\_\_\_,  
(Patient's Name)

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

Initials: \_\_\_\_\_

2. My 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 Isotretinoin. These have been explained to me. These side effects include serious birth defects in babies of pregnant females. (Note: There is a second Informed Consent form for female patients concerning birth defects.)

Initials: \_\_\_\_\_

4. I understand that some patients, while taking Isotretinoin or soon after stopping Isotretinoin, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Isotretinoin 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. No one knows if Isotretinoin caused these behaviors or if they would have happened even if the person did not take Isotretinoin. Some people have had other signs of depression while taking Isotretinoin (see #7 below).

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

6. Before I start taking Isotretinoin, 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 Isotretinoin, I agree to stop using Isotretinoin and tell my prescriber right away if any of the following happen. I:

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

I now authorize my prescriber \_\_\_\_\_ to begin my treatment with Isotretinoin.

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Parent/Guardian Signature (if under age 18): \_\_\_\_\_

Date: \_\_\_\_\_

Patient Name (print) \_\_\_\_\_

Patient Address \_\_\_\_\_

Telephone \_\_\_\_\_

I have:

- fully explained to the patient, \_\_\_\_\_, the nature and purpose of Isotretinoin treatment, including its benefits and risks
- given the patient the appropriate educational materials, *Pregnancy Avoidance Program (PAP)*, for Isotretinoin and asked the patient if he/she has any questions regarding his/her treatment with Isotretinoin
- answered those questions to the best of my ability
- placed the yellow self-adhesive Isotretinoin Qualification Sticker on the prescription.

Prescriber Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## MEDICATION GUIDE:

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

Isotretinoin is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics. However, Isotretinoin can cause serious side effects. Before starting Isotretinoin, discuss with your prescriber how bad your acne is, the possible benefits of ISOTRETINOIN, and its possible side effects, to decide if Isotretinoin 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 Isotretinoin.

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

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

- 2. Mental problems and suicide.** Some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental problems. Symptoms of these problems include sad, "anxious" or empty mood, irritability, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking isotretinoin 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. No one knows if isotretinoin caused these behaviors or if they would have happened even if the person did not take isotretinoin.

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

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

### **What are the important warnings for females taking Isotretinoin?**

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

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

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

While you are taking Isotretinoin, 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 Isotretinoin, 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 Isotretinoin treatment.

**If you have sex at any time without using 2 forms of effective birth control, get pregnant, or miss your period, stop using Isotretinoin 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 ISOTRETINOIN 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 than usual
- Have a change in your appetite or body weight
- Have trouble concentrating
- Withdraw from your friends or family
- Feel like you have no energy
- Have feelings of worthlessness or inappropriate guilt
- Start having thoughts about hurting yourself or taking your own life (suicidal thoughts)

#### **What is Isotretinoin?**

Isotretinoin is used to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. In severe 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 Isotretinoin can have serious side effects, you should talk with your prescriber about all of the possible treatments for your acne, and whether Isotretinoin's possible benefits outweigh its possible risks.

#### **Who should not take Isotretinoin?**

- **Do not take Isotretinoin if you are pregnant, plan to become pregnant, or become pregnant during Isotretinoin treatment.** Isotretinoin causes severe birth defects. All females should read the section "What are the important warnings for females taking Isotretinoin?" for more information and warnings about Isotretinoin and pregnancy.
- Do not take Isotretinoin 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, 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 Isotretinoin, but your prescriber needs this information to discuss if Isotretinoin is right for you.

#### **How should I take Isotretinoin?**

- You will get no more than a 1 month supply of Isotretinoin 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 ISOTRETINOIN you take has been specially chosen for you and may change during treatment.
- You will take ISOTRETINOIN 2 times a day with a meal, unless your prescriber tells you otherwise. Swallow your Isotretinoin 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 Isotretinoin'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 Isotretinoin?**

- **Do not get pregnant** while taking Isotretinoin. See "What is the most important information I should know about Isotretinoin?" and "What are the important warnings for females taking Isotretinoin?"
- **Do not breast feed** while taking Isotretinoin and for 1 month after stopping Isotretinoin. We do not know if Isotretinoin can pass through your milk and harm the baby.
- **Do not give blood** while you take Isotretinoin and for 1 month after stopping Isotretinoin. If someone who is pregnant gets your donated blood, her baby may be exposed to Isotretinoin 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 Isotretinoin. 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 Isotretinoin and for at least 6 months after you stop.** Isotretinoin 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. Isotretinoin may make your skin more sensitive to light.
- **Do not use birth control pills that do not contain estrogen ("minipills").** They may not work while you take Isotretinoin. 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.
- **Do not share Isotretinoin with other people.** It can cause birth defects and other serious health problems.
- **Do not take Isotretinoin with antibiotics unless you talk to your prescriber.** For some antibiotics, you may have to stop taking Isotretinoin 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 Isotretinoin?**

**Isotretinoin has possible serious side effects**

- **Isotretinoin can cause birth defects, premature births, and death in babies** whose mothers took Isotretinoin while they were pregnant. See “What is the most important information I should know about Isotretinoin?” and “What are the important warnings for females taking Isotretinoin?”
- **Serious mental health problems.** See “What is the most important information I should know about Isotretinoin?”
- **Serious brain problems.** Isotretinoin can increase the pressure in your brain. This can lead to permanent loss of sight, or in rare cases, death. Stop taking Isotretinoin and call your prescriber right away if you get any of these signs of increased brain pressure: bad headache, blurred vision, dizziness, nausea, or vomiting. Also, some patients taking isotretinoin have had seizures (convulsions) or stroke.
- **Abdomen (stomach area) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, and bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Isotretinoin. Stop taking Isotretinoin 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.** Isotretinoin 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 Isotretinoin. Tell your prescriber if you develop pain. Muscle weakness with or without pain can be a sign of serious muscle damage. If this happens stop taking Isotretinoin and call your prescriber right away. If a bone breaks, tell your prescriber you take Isotretinoin. No one knows if taking Isotretinoin for acne will reduce bone healing or stunt growth.
- **Hearing problems.** Some people taking isotretinoin have developed hearing problems. It is possible that hearing loss can be permanent. Stop using Isotretinoin and call your prescriber if your hearing gets worse or if you have ringing in your ears.
- **Vision problems.** While taking Isotretinoin you may develop a sudden inability to see in the dark, so driving at night can be dangerous. This condition usually clears

up after you stop taking Isotretinoin, but it may be permanent. Other serious eye effects can occur. Stop taking Isotretinoin and call your prescriber right away if you have any problems with your vision or dryness of the eyes that is painful or constant.

- **Lipid (fats and cholesterol in blood) problems.** Many people taking Isotretinoin develop high levels of cholesterol and other fats in their blood. This can be a serious problem. Return to your prescriber for blood tests to check your lipids and to get any needed treatment. These problems generally go away when Isotretinoin treatment is finished.
- **Allergic reactions.** In some people, Isotretinoin can cause serious allergic reactions. Stop taking Isotretinoin and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Isotretinoin and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Isotretinoin 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 Isotretinoin 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 Isotretinoin.

#### **Isotretinoin has less serious possible side effects**

The common less serious side effects of Isotretinoin 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 Isotretinoin and after therapy. Sometimes, people's acne may get worse for a while. They should continue taking Isotretinoin unless told to stop by their prescriber.

These are not all of Isotretinoin'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 Isotretinoin. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about Isotretinoin, ask your prescriber. Do not use Isotretinoin for a condition for which it was not prescribed.

**Active Ingredient: Isotretinoin.**

Inactive Ingredients: butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil, hydrogenated vegetable oil, iron oxide black, soybean oil and white wax. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg - iron oxide (red) and titanium dioxide; 20 mg - FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 30 mg - FD&C Yellow No. 6, and titanium dioxide; 40 mg -D&C Yellow No. 10, FD&C Yellow No. 6, and titanium dioxide.

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

Rx only

**ATTACHMENT C**



**ACCUTANE®**  
(isotretinoin)  
CAPSULES

**CAUSES BIRTH DEFECTS**



**AVOID PREGNANCY**

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

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

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including micropthalmia); facial dysmorphia; cleft palate.

Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

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

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

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

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

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

- 1) Read the booklet entitled *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) *Guide to Best Practices*.
- 2) Sign and return the completed S.M.A.R.T. *Letter of Understanding* containing the following Prescriber Checklist:
  - I know the risk and severity of fetal injury/birth defects from Accutane
  - I know how to diagnose and treat the various presentations of acne
  - I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy
  - It is the informed patient's responsibility to avoid pregnancy during Accutane therapy and for 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. The manufacturer will make available urine pregnancy test kits for female Accutane patients for the initial, second and monthly testing during therapy.
- **Must** have selected and 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 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 injectable/implantable contraceptive 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.

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:**

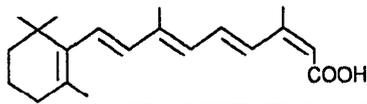
- **IN NO MORE THAN A 30-DAY SUPPLY**

- ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER
- WRITTEN WITHIN THE PREVIOUS 7 DAYS
- REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER
- NO TELEPHONE OR COMPUTERIZED PRESCRIPTIONS ARE PERMITTED.

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

**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.<sup>1</sup>

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

Accutane 2 x 40 mg Capsules	AUC <sub>0-∞</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)
Fed	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

**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. After multiple oral dose administration of isotretinoin to adult cystic acne patients ( $\geq 18$  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. Given its abundance and degree of retinoid activity, it is most likely that 4-*oxo*-isotretinoin is a significant contributor to the activity of Accutane.

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

*Elimination:* Following oral administration of an 80 mg dose of  $^{14}\text{C}$ -isotretinoin as a liquid suspension,  $^{14}\text{C}$ -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  $\pm$  SD elimination half-lives ( $t_{1/2}$ ) of isotretinoin and 4-oxo-isotretinoin were  $21.0 \pm 8.2$  hours and  $24.0 \pm 5.3$  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.

**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,<sup>2</sup> means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Accutane is indicated only for those females who are not pregnant, because Accutane can cause severe birth defects (see boxed CONTRAINDICATIONS AND WARNINGS).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.<sup>1,3,4</sup> 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: 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 and suicide. 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 have been reported in patients treated with Accutane. Marked elevations of serum triglycerides in excess of 800 mg/dL 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.<sup>5</sup>

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

The cardiovascular consequences of hypertriglyceridemia associated with Accutane are unknown. ***Animal Studies:*** In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface

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

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

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

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

*Skeletal: 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.<sup>6</sup> 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.

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

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

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

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

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

The following further describes each component:

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

The Prescriber Checklist attests that Accutane prescribers know the risk and severity of injury/birth defects from Accutane; know how to diagnose and treat the various presentations of acne; know the risk factors for unplanned pregnancy and the effective

measures for avoidance; will refer the patient for, or provide, detailed pregnancy prevention counseling to help the patient have knowledge and tools needed to fulfill their ultimate responsibility to avoid becoming pregnant; understand and properly use throughout the Accutane treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and use of qualified prescriptions with the yellow self-adhesive Accutane Qualification Sticker.

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

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

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

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

***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 videotape provided by the manufacturer to the prescriber. It includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another 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*).
- Patients should be informed that they must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events.
- Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane.
- Patients should be reminded to take Accutane with a meal (see DOSAGE AND ADMINISTRATION). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.

- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.
- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS: *Skin and Appendages*).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted (see ADVERSE REACTIONS: *Musculoskeletal*). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see *Laboratory Tests*: CPK).
- 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 injectable/implantable contraceptive products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see boxed CONTRAINDICATIONS AND WARNINGS).
- *Phenytoin:* Accutane has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme.

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

***Laboratory Tests:***

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

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

- *Lipids*: Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see WARNINGS: *Lipids*).
- *Liver Function Tests*: Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS: *Hepatotoxicity*).
- *Glucose*: Some patients receiving Accutane have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane therapy, although no causal relationship has been established.
- *CPK*: Some patients undergoing vigorous physical activity while on Accutane therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity.

*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.

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

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

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

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

*Cardiovascular:* palpitation, tachycardia, vascular thrombotic disease, stroke

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

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

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

*Musculoskeletal:* skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure (see WARNINGS: *Skeletal*), mild to moderate musculoskeletal symptoms including 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 (see WARNINGS: *Psychiatric Disorders*), emotional instability

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

*Reproductive System:* abnormal menses

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

*Skin and Appendages:* acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,<sup>7</sup> 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<sub>50</sub> of isotretinoin is greater than 4000 mg/kg in rats and mice (>600 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the rat dose for total body surface area and >300 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without apparent residual effects.

Accutane causes serious birth defects at any dosage (see boxed CONTRAINDICATIONS AND WARNINGS). Females of childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive

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

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

The recommended dosage range for Accutane is 0.5 to 1.0 mg/kg/day given in two divided doses for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,<sup>8</sup> 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. 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 (see WARNINGS: *Skeletal: Hyperostosis and Premature Epiphyseal Closure*).

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

**Table 2. Accutane Dosing by Body Weight (Based on Administration With Food)**

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

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

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

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

**REFERENCES:**

1. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remissions of cystic and conglobate acne with 13-*cis*-retinoic acid. *N Engl J Med* 300:329-333, 1979.
2. Pochi PE, Shalita AR, Strauss

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

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

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

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

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

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

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, 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 and pregnancy testing 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 video about contraception. I was told about a confidential counseling line that I may call for more information about birth control. I have received information on emergency contraception (birth control).

Initial: \_\_\_\_\_

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

Initial: \_\_\_\_\_

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

Initial: \_\_\_\_\_

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

- have had 2 negative urine or serum pregnancy tests before receiving the initial Accutane prescription. I must have a negative result from a urine or serum pregnancy test repeated each month prior to my receiving each subsequent prescription.
- have selected and committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen

method, or I have undergone a hysterectomy. I must use 2 forms of contraception for at least 1 month prior to initiation of Accutane therapy, during therapy, and for 1 month after discontinuing therapy. I must receive counseling, repeated on a monthly basis, about contraception and behaviors associated with an increased risk of pregnancy.

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

Initial: \_\_\_\_\_

**My prescriber has answered all my questions about Accutane and I understand that 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: \_\_\_\_\_

Please print: Patient name and address \_\_\_\_\_

\_\_\_\_\_ Telephone \_\_\_\_\_

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

Prescriber signature: \_\_\_\_\_ Date: \_\_\_\_\_

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

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

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

1. I, \_\_\_\_\_,  
(Patient's Name)

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Accutane. Some people have had other signs of depression while taking Accutane (see #7 below).

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

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

Initials: \_\_\_\_\_

I now authorize my prescriber \_\_\_\_\_ to begin my treatment with Accutane.

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

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

Patient Name (print) \_\_\_\_\_

Patient address \_\_\_\_\_ Telephone (\_\_\_\_.\_\_\_\_.\_\_\_\_)

I have:

- fully explained to the patient, \_\_\_\_\_, the nature and purpose of Accutane treatment, including its benefits and risks

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

Prescriber Signature: \_\_\_\_\_ Date: \_\_\_\_\_

## **MEDICATION GUIDE:**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**What are the signs of mental problems?**

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

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

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

**What is Accutane?**

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

**Who should not take Accutane?**

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

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

#### **How should I take Accutane?**

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

#### **What should I avoid while taking Accutane?**

- **Do not get pregnant** while taking Accutane. See "What is the most important information I should know about Accutane?" and "What are the important warnings for females taking Accutane?"
- **Do not breast feed** while taking Accutane and for 1 month after stopping Accutane. We do not know if Accutane can pass through your milk and harm the baby.
- **Do not give blood** while you take Accutane and for 1 month after stopping Accutane. If someone who is pregnant gets your donated blood, her baby may be exposed to Accutane and may be born with birth defects.
- **Do not take vitamin A** supplements. Vitamin A in high doses has many of the same side effects as Accutane. Taking both together may increase your chance of getting side effects.

- **Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using Accutane and for at least 6 months after you stop.** Accutane can increase your chance of scarring from these procedures. Check with your prescriber for advice about when you can have cosmetic procedures.
- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. Accutane may make your skin more sensitive to light.
- **Do not use birth control pills that do not contain estrogen (“minipills”).** They may not work while you take Accutane. Ask your prescriber or pharmacist if you are not sure what type you are using.
- **Talk with your doctor if you plan to take other drugs or herbal products.** This is especially important for patients using birth control pills and other hormonal types of birth control because the birth control may not work as effectively if you are taking certain drugs or herbal products. You should not take the herbal supplement St. John’s Wort because this herbal supplement may make birth control pills not work as effectively.
- **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. 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. If a bone breaks, tell your provider you take Accutane. No one knows if taking Accutane for acne will reduce bone healing or stunt growth.
- **Hearing problems.** Some people taking Accutane have developed hearing problems. It is possible that hearing loss can be permanent. Stop using Accutane and call your prescriber if your hearing gets worse or if you have ringing in your ears.
- **Vision problems.** While taking Accutane you may develop a sudden inability to see in the dark, so driving at night can be dangerous. This condition usually clears up after you stop taking Accutane, but it may be permanent. Other serious eye effects can occur. Stop taking Accutane and call your prescriber right away if you have any problems with your vision or dryness of the eyes that is painful or constant.
- **Lipid (fats and cholesterol in blood) problems.** Many people taking Accutane develop high levels of cholesterol and other fats in their blood. This can be a serious problem. Return to your prescriber for blood tests to check your lipids and to get any needed treatment. These problems generally go away when Accutane treatment is finished.
- **Allergic reactions.** In some people, Accutane can cause serious allergic reactions. Stop taking Accutane and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane and call your prescriber if you develop a fever, rash, or red patches or bruises on your legs.
- **Signs of other possibly serious problems.** Accutane may cause other problems. Tell your prescriber if you have trouble breathing (shortness of breath), are fainting, are very thirsty or urinate a lot, feel weak, have leg swelling, convulsions, slurred speech, problems moving, or any other serious or unusual problems. Frequent urination and thirst can be signs of blood sugar problems.

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.



**Pharmaceuticals**

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