

BARR LABORATORIES, INC.

Claravis (isotretinoin capsules, USP)

## CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

## CONTRAINDICATIONS AND WARNINGS

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

Birth defects which have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, thymus and parathyroid. Cases of 10 or less total to 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

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

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

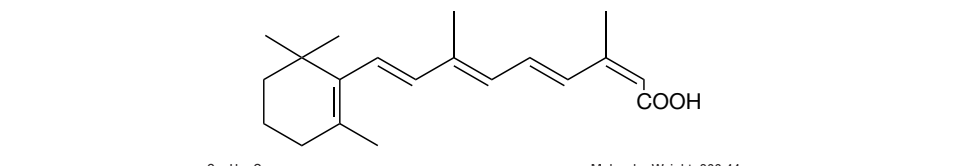
## Special Precautions Required

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

## Table 1. Monthly Required IPLEDGE Interactions

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

**DESCRIPTION:** Claravis™ (isotretinoin), a retinoid, is available in 10-mg, 20-mg and 40-mg hard gelatin capsules for oral administration. 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. The structural formula is:



Each capsule contains the following inactive ingredients: butylated hydroxyanisole, edetate disodium, gelatin, hydrogenated vegetable oil, polysorbate 80, soybean oil, titanium dioxide, white wax (beeswax), and vitamin E.

In addition, the 10 mg capsule contains black iron oxide and FD&C yellow no. 6. The 20 mg capsule contains black iron oxide, red iron oxide and yellow iron oxide. The 40 mg capsule contains FD&C yellow no. 6.

The edible imprinting ink contains: 10 mg strength, D&C red 7, calcium lake, ethylene glycol monochloro ether, FD&C yellow no. 6, pharmaceutical shellac, and titanium dioxide; 20 mg strength, ammonium hydroxide, pharmaceutical grade, propylene glycol, simethicone and titanium dioxide; the 40 mg strength, ammonium hydroxide, FD&C blue no. 2, iron oxide black, propylene glycol, and shellac, glaze.

## 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 Claravis, 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 Claravis under fasted and fed conditions. Both peak plasma concentration (C<sub>max</sub>) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with Claravis given under fasted conditions (see Table 2). The observed elimination half-life was unchanged. This lack of change in half-life suggests that food increases the bioavailability of isotretinoin without affecting its disposition. The time to peak concentration (T<sub>max</sub>) was also increased with food and may be related to a longer absorption phase. Therefore, Claravis 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.

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

\* Eating a standardized high-fat meal

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

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

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. The metabolites possess retinoid activity that is in some *in vitro* models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (> 2 years), the exposure of patients to 4-*oxo*-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

***In vivo* studies** indicate that the primary P450 isozymes involved in isotretinoin metabolism are C2C, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates. The elimination half-life of isotretinoin is approximately 12 to 17 hours. The elimination half-life of 4-*oxo*-isotretinoin is approximately 12 to 17 hours. Following oral administration of an 80 mg dose of <sup>14</sup>C-isotretinoin as a liquid suspension, <sup>14</sup>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 ± SD elimination half-lives (t<sub>1/2</sub>) of isotretinoin and 4-*oxo*-isotretinoin were 21.0 ± 8.2 hours and 21.0 ± 8.2 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43 in patients with cystic acne.

## Special Patient Populations:

Pediatric pharmacokinetic information related to the use of isotretinoin after single and multiple doses is approved for Hoffmann La-Roche's isotretinoin capsules. However, due to Hoffmann La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

## INDICATIONS AND USAGE:

## Severe Recalcitrant Nodular Acne:

Claravis (isotretinoin capsules, USP) is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules, because of their size, may become suppurative or hemorrhagic. "Severe" is, by definition, "many" as opposed to "few or several." Because of significant adverse effects associated with its use, Claravis should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Claravis is indicated only for those female patients who are not pregnant, because Claravis 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>1,3-14</sup> 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 Claravis. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see WARNINGS: Skeletal; Bone Mineral Density, Hyperostosis and Premature Epiphyseal Closure).

## CONTRAINDICATIONS:

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

## Allergic Reactions:

Claravis is contraindicated in patients who are hypersensitive to this medication or to any of its components. (see PRECAUTIONS: Hypersensitivity).

## WARNINGS:

## Psychiatric Disorders:

Claravis may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). Prescribers should read the brochure "Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin." Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Claravis therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary.

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**Signs and symptoms of depression, as described in the brochure ("Recognizing Psychiatric Disorders in Adolescents and Young Adults"), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop Claravis and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Claravis therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether Claravis therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of isotretinoin therapy.**

## Pseudotumor Cerebri:

Claravis 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 papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilloedema and, if present, should be told to discontinue Claravis 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. Claravis should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

## Lipids:

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with Claravis. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving Claravis 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 Claravis 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 Claravis.

Blood lipid determinations should be performed before Claravis is given and then at intervals until the lipid response to Claravis 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 Claravis therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Claravis therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS: Laboratory Tests).

The cardiovascular system of hypertensive patients associated with Claravis use is 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 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 Claravis; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanisms) and causality for this event have not been established. Patients who experience tinnitus or hearing impairment should discontinue Claravis treatment and be referred for specialized care for further evaluation (see ADVERSE REACTIONS: Special Senses).

## Hepatotoxicity:

Hepatotoxicity considered to be possibly or probably related to Claravis 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 Claravis, the drug should be discontinued and the etiology further investigated.

## Inflammatory Bowel Disease:

Claravis 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 Claravis treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Claravis immediately (see ADVERSE REACTIONS: Gastrointestinal).

## Skeletal:

**Bone Mineral Density:** Effects of multiple courses of Claravis on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a second course of therapy with Claravis for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >-4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >-4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >-5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >-5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 8 of patients (82.5%).

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

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

**Hyperostosis:** A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization.<sup>5</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 courses of therapy for acne are unknown.

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

**Premature Epiphyseal Closure:** There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Claravis. The clinical course of cases of Claravis on epiphyseal closure is unknown.

## Vision Impairment:

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

**Cornal Opacities:** Cornal opacities have occurred in patients receiving Claravis 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 Claravis have either completely resolved or were resolved after discontinuation of therapy and returning the IPLEDGE wholesaler agreement that affirms they will comply with all IPLEDGE requirements for distribution of isotretinoin. These include:

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

• Providing product flow data to manufacturer (or delegate) as detailed in the wholesaler's agreement

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

- I will not sell, buy, borrow, or otherwise transfer isotretinoin to any other name than to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if registration is revoked by the manufacturer or if the pharmacy chooses to not reactivate annually.
- I will not fill Claravis for any party other than a qualified patient.

To dispense Claravis, the pharmacist must:

- 1) be trained by the Responsible Site Pharmacist concerning the IPLEDGE program requirements.
- 2) obtain authorization from the IPLEDGE program via the internet ([www.ipledgeprogram.com](http://www.ipledgeprogram.com)) or telephone (1-866-495-0654) for every Claravis prescription.
- 3) write the Risk Management Authorization (RMA) number on the prescription.

Claravis must only be dispensed:

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

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

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

A description of the IPLEDGE program educational materials available with IPLEDGE is provided below. The main goal of these educational materials is to explain the IPLEDGE program requirements for prescribers, pharmacists, and patients.

- 1) **The IPLEDGE Program Guide to Best Practices for Isotretinoin** includes: isotretinoin teratogenic potential, information on pregnancy testing, and the method to complete a qualified Claravis prescription.
- 2) **The IPLEDGE Program Prescriber Contraception Counseling Guide** includes: specific information about effective contraception, the limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure and pregnancy and the methods to evaluate pregnancy risk.
- 3) **The IPLEDGE Program Pharmacist Guide for Isotretinoin** includes: isotretinoin teratogenic potential and the method to obtain authorization to dispense an isotretinoin prescription.
- 4) The IPLEDGE program is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The IPLEDGE program includes information on the risk and benefits of isotretinoin which is linked to the Medication Guide dispensed by the pharmacist with each isotretinoin prescription.
- 5) Female patients not of childbearing potential and male patients, and female patients of childbearing potential are provided with separate booklets. Each booklet contains information on isotretinoin therapy including precautions and warnings, a Patient Information/Informed Consent (for all patients) form for all patients, and a toll-free line, which provides isotretinoin information in 2 languages.
- 6) The booklet for female patients not of childbearing potential and male patients, **The IPLEDGE Program Guide to Isotretinoin for Male Patients & Female Patients Who Cannot Get Pregnant** (or delegate) includes information about the risk of potential birth defects if the fetus is exposed to isotretinoin.
- 7) The booklet for female patients of childbearing potential, **The IPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant**, includes a referral program that offers female patients free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; and a second Patient Information/Informed Consent form.
- 8) The booklet, **The IPLEDGE Program Birth Control Workbook** includes information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, the rates of possible contraceptive failure and a toll-free contraception counseling line.
- 9) In addition, there is a patient education DVD with the following videos — "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin" (see Information for Patients).

## General:

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

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

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

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

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

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

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

If the patient has not reported heterosexual intercourse at any time 1 month before, during, or 1 month after therapy, she must:

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

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

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

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

Using two forms of contraception simultaneously substantially reduces the chances that a female will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Claravis (see PRECAUTIONS: Drug Interactions). Although hormonal contraceptives are highly effective, Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives on reports of breakthrough bleeding in patients who started St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

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

## All Patients:

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

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

## Female Patients of Childbearing Potential:

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

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

## Pharmacists:

To dispense Claravis, pharmacies must be registered and activated with the pregnancy

## Clarithiv (isotretinoin capsules, USP)

**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 Clariv.

### Pediatric Use:

The use of isotretinoin in pediatric patients less than 12 years of age has not been studied. The use of isotretinoin for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see PRECAUTIONS: General).

Evidence supporting the use of isotretinoin in this age group for severe recalcitrant nodular acne is approved for Hoffmann-La-Roche's isotretinoin capsules. However, due to Hoffmann-La-Roche's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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

In an open-label clinical trial (N=217) of a single course of therapy with Clariv for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >=4% and total hip change >=5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Seven (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases but increases (adjusted for body mass index). Nine patients (4.1%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density of up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 9 patients (62.5%).

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

### Geriatric Use:

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

### ADVERSE REACTIONS:

#### Clinical Trials and Postmarketing Surveillance:

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

### Dose Relationship:

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

**Body as a Whole:** allergic reactions, including vasculitis, systemic hypersensitivity (see PRECAUTIONS: Hypersensitivity), edema, fatigue, lymphadenopathy, weight loss. **Cardiovascular:** palpitation, tachycardia, vascular thrombotic disease, stroke.

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

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

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

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

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

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

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with 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, 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, pruritis, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, sweating, urticaria, vasculitis (including Wegener's granulomatosis; see PRECAUTIONS: Hypersensitivity), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see PRECAUTIONS: Information for Patients).

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

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

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

### Laboratory:

Elevation of plasma triglycerides (see WARNINGS: Lipids), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment. Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGT or LDH (see WARNINGS: Hepatotoxicity).

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

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

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

### OVERDOSEAGE:

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, cheilitis, abdominal pain, headache, dizziness and ataxia. These symptoms quickly resolve without apparent residual effects.

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

### DOSSAGE AND ADMINISTRATION:

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

The recommended dosage range for Clariv is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5 and 1 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. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Clariv 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 Clariv 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 between retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of Clariv, even in low doses, has not been studied, and is not recommended. It is important that Clariv be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Clariv on bone loss is unknown (see WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis and Premature Epiphyseal Closure).

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

Table 3. Clariv Dosing by Body Weight (Based on Administration With Food)				
Body Weight	pounds		Total Weight	
	0.5 mg/kg	1 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

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

INFORMATION FOR PHARMACISTS:				
Access the iPLEDGE system via the internet (www.ipledegsprogram.com) or telephone (1-866-495-0654) to obtain an authorization and the "do not dispense to patient after" date. Clariv must only be dispensed in no more than a 30-day supply.				
<b>REFILLS REQUIRE A NEW PRESCRIPTION AND A NEW AUTHORIZATION FROM THE iPLEDGE SYSTEM.</b>				
A Clariv Medication Guide must be given to the patient each time Clariv is dispensed, as required by law. This Clariv Medication Guide is an important part of the risk management program for the patient.				
<b>HOW SUPPLIED:</b>				
<b>Clariv®</b> (isotretinoin capsules, USP) are available as:				
10 mg:	Light gray opaque cap and light gray body filled with yellow oily dispersion.			
	Imprinted in red ink <b>barr</b> 934.	Available as cartons of 30 capsules containing 3 prescription blister packs of 10 capsules: NDC 0555-1054-86		
	Available as cartons of 100 capsules containing 10 prescription blister packs of 10 capsules: NDC 0555-1054-56			
20 mg:	Brown orange opaque cap and brown opaque body filled with yellow oily dispersion.			
	Imprinted in white ink <b>barr</b> /935.	Available as cartons of 30 capsules containing 3 prescription blister packs of 10 capsules: NDC 0555-1055-86		
	Available as cartons of 100 capsules containing 10 prescription blister packs of 10 capsules: NDC 0555-1055-56			
40 mg:	Light orange opaque cap and light orange opaque body filled with yellow oily dispersion.			
	Imprinted in black ink <b>barr</b> /936.	Available as cartons of 30 capsules containing 3 prescription blister packs of 10 capsules: NDC 0555-1057-86		
	Available as cartons of 100 capsules containing 10 prescription blister packs of 10 capsules: NDC 0555-1057-56			

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from light.

## Clarithiv (isotretinoin capsules, USP)

### REFERENCES:

- 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, Straliet 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, Madson KC, Pennes DR, Mariel 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, Rapin RP, Shalita AR, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. *J Am Acad Dermatol* 10:490-496, 1984.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- have had 2 negative urine or blood pregnancy tests before receiving the first isotretinoin prescription. The second test must be done in a lab. I must have a negative result from a urine or blood pregnancy test done in a lab repeated each month before I receive another isotretinoin prescription.
- have chosen and agreed to use 2 forms of effective birth control at the same time. At least 1 method must be a primary form of birth control, **unless I have chosen never to have sexual contact with a male (abstinence)**, or I have undergone a hysterectomy. I must use 2 forms of birth control for at least 1 month before I start isotretinoin therapy, during therapy, and for 1 month after stopping therapy. I must receive counseling, repeated on a monthly basis, about birth control and behaviors associated with an increased risk of pregnancy.
- have signed a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) that contains warnings about the chance of possible birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.
- have been informed of and understand the purpose and importance of providing information to the iPLEDGE program and I became pregnant while taking isotretinoin or within 1 month of the last dose. I agree to be contacted by the iPLEDGE program and be asked questions about my pregnancy.
- have interacted with the iPLEDGE program before starting isotretinoin and on a monthly basis to answer questions on the program requirements and to enter my two chosen forms of birth control.

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

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

Doctor Signature: \_\_\_\_\_ Date: \_\_\_\_\_

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7. Once I start taking isotretinoin, I agree to stop using isotretinoin and tell my doctor right away if any of the following signs and symptoms of depression or psychosis happen to me:

- Start to feel sad or have crying spells
- Lose interest in activities I once enjoyed
- Sleep too much or have trouble sleeping
- Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- Have a change in my appetite or body weight
- Have trouble concentrating
- Withdraw from my friends or family
- Feel like I have no energy
- Have feelings of worthlessness or guilt
- Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
- Start acting on dangerous impulses
- Start seeing or hearing things that are not real

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

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

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

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

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

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

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

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

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

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

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

I now allow my doctor \_\_\_\_\_ to begin my treatment with isotretinoin.

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

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

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

Patient Address \_\_\_\_\_ Telephone (\_\_\_\_\_) \_\_\_\_\_

I have:

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

Doctor Signature: \_\_\_\_\_ Date: \_\_\_\_\_