

SOTRET®
ISOTRETINOIN CAPSULES, USP
Rx only



CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS
Sotret 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 isotretinoin capsules 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, and thymus and parathyroid glands. Cases of IQ scores less than 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 anopia, microplasia, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphism; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral atrophy, 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 mentioned.
If pregnancy does occur during treatment of a female patient who is taking isotretinoin capsules, isotretinoin capsules must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.
Special Prescribing Requirements
Because of isotretinoin's teratogenicity and to minimize fetal exposure, Sotret is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called IPLEDGE. Sotret must only be prescribed by prescribers who are registered and activated with the IPLEDGE program. Sotret capsules 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).

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

DESCRIPTION
Isotretinoin, a retinoid, is available as Sotret in 10 mg, 20 mg, 30 mg, and 40 mg soft gelatin capsules for oral administration. Each capsule contains butylated hydroxyanisole, edetate disodium hydroxide, 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. 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 Sotret, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.¹
Pharmacokinetics
Absorption
Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. In a crossover study, 74 healthy adult subjects received a single 80 mg oral dose (2 x 40 mg capsules) of isotretinoin capsules under fasted and fed conditions. The mean plasma concentration (C_{max}) and total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with isotretinoin capsules 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 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, Sotret 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.

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

* Eating a standardized high-fat meal.

Distribution
Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.
Metabolism
Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-oxo-isotretinoin, 13-*cis*-isotretinoin, and 4-oxo-retinoic acid (4-oxo-retinoic acid). 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 is further oxidized to 4-oxo-retinoic acid.
After a single 80 mg oral dose of isotretinoin capsules to 74 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.
All of these metabolites possess retinoid activity that is in some *in vitro* models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (≥ 18 years), the exposure of patients to 4-oxo-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.
In 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, which are then excreted in urine and feces.
Elimination
Following oral administration of an 80 mg dose of ¹⁴C-isotretinoin as a liquid suspension, ¹⁴C-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, in addition to excretion in the feces, the elimination half-lives (t_{1/2}) of isotretinoin and 4-oxo-isotretinoin were 21.0 ± 8.2 hours and 24.0 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 1.05 to 1.45 in patients with cystic acne.

Special Patient Populations

Pediatric Patients
Pediatric pharmacokinetic information related to the use of isotretinoin capsules 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
Sotret 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, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Sotret should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy. Sotret should be used only in patients who are not pregnant, because Sotret 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. 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 capsules. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see WARNINGS: Skeletal: Bone Mineral Density, Hypersensitivity, and Premature Epiphyseal Closure).
CONTRAINDICATIONS
Pregnancy: Category X. See Boxed CONTRAINDICATIONS AND WARNINGS.
Allergic Reactions
Sotret is contraindicated in patients who are hypersensitive to this medication or to any of its components. Sotret 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
Sotret 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 Sotret 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. Signs and symptoms of depression, as described in the brochure *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*, include: persistent feelings of hopelessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, weight gain or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop Sotret 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 Sotret therapy may be indicated; 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 Sotret therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of isotretinoin therapy.

Pseudotumor Cerebri
Isotretinoin capsule 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, they should be told to discontinue Sotret 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. Sotret should be stopped if hypertriglyceridemia Sotret patients who have not completed skeletal growth (see WARNINGS: Skeletal: Bone Mineral Density, Hypersensitivity, and Premature Epiphyseal Closure).
Lipids
Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with isotretinoin capsules. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving isotretinoin capsules 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 capsules 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 capsules.³
Blood lipid determinations should be performed before Sotret is given and then at intervals until the lipid response to Sotret 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 Sotret therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Sotret therapy is instituted, more frequent checks of serum values for lipids and blood sugar are recommended (see PRECAUTIONS: Laboratory Tests).
The cardiovascular consequences of hypertriglyceridemia associated with Sotret 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 isotretinoin capsules; 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 Sotret immediately 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 isotretinoin capsules therapy has been reported. Additional, 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 Sotret, the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease
Isotretinoin capsules have 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 isotretinoin capsules treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Sotret immediately (see ADVERSE REACTIONS: Gastrointestinal).
Skeletal
Bone Mineral Density
Effects of multiple courses of Sotret 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=21) of a single course of therapy with isotretinoin 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 increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (75%) 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 (43%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.5%) 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 increased 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 -1.0% to -0.7%) in 5 of 6 patients (82.5%).
In a separate open-label extension study of 10 patients, ages 13-18 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 PRECAUTIONS: Pediatric Use).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been reported in the isotretinoin population. While a causal relationship has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Sotret be given at the recommended doses for no longer than the recommended duration.
Hypersensitivity
A high prevalence of skeletal hypostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hypostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization.¹ Minimal skeletal hypostosis and calcification of ligaments in the hands were observed in an unadjusted data. Sixteen (75%) 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 (43%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.5%) 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 increased 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 -1.0% to -0.7%) in 5 of 6 patients (82.5%).
In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hypersensitivity was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of isotretinoin capsules given in two divided doses. Hypersensitivity 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 isotretinoin capsules. The effect of multiple courses of Sotret on epiphyseal closure is unknown.

Visual Impairment
Visual problems should be carefully monitored. All Sotret patients experiencing visual difficulties should discontinue Sotret treatment and have an ophthalmological examination (see ADVERSE REACTIONS: Special Senses).
Corneal Opacities
Corneal opacities have occurred in patients receiving isotretinoin capsules 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 isotretinoin capsules 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 isotretinoin capsules therapy and in some instances the vision has persisted after therapy was discontinued. Because the mechanism of action was not defined, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

PRECAUTIONS
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Wholesalers:
For the purpose of the IPLEDGE program, the term wholesaler refers to wholesaler, distributor, and/or chain pharmacy distributor. To distribute Sotret, wholesalers must be registered with IPLEDGE, and must meet all IPLEDGE requirements for wholesaler registration. Wholesalers must register with IPLEDGE by signing 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 IPLEDGE program prescribers
• 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
• Providing inspection of wholesaler records for verification of compliance with the IPLEDGE program by the isotretinoin manufacturer (or delegate)
• Returning to the manufacturer (or delegate) any undistributed product if registration is revoked by the manufacturer or if the wholesaler chooses to not reregister annually
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• Registering prior to distributing isotretinoin and reregistering annually thereafter
• Distributing only FDA approved isotretinoin product
• Only shipping isotretinoin to IPLEDGE program prescribers
• 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
• Providing inspection of wholesaler records for verification of compliance with the IPLEDGE program by the isotretinoin manufacturer (or delegate)
• Returning to the manufacturer (or delegate) any undistributed product if registration is revoked by the manufacturer or if the wholesaler chooses to not reregister annually
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