SOTRET

(Isotretinoin Capsules BP)
(For oral administration)

Pregnancy
Isotretinoin is teratogenic. Its use is therefore contraindicated not only in pregnant women and women who could become pregnant during and for one month after ending treatment, but in all women of childbearing potential. The danger of bearing a malformed child is extremely high if isotretinoin is taken at any dose before or during pregnancy, even for only a short time. Every unborn child is at risk of malformation.
Isotretinoin is contraindicated in any woman of childbearing age unless all the following conditions are met:

1. Isotretinoin must be clearly indicated.
2. It is certain that the patient understands and will follow her doctor's orders.
3. She is able to carry out the obligatory contraceptives measures reliably and regularly.
4. Any woman of childbearing potential who is treated with isotretinoin must practice effective contraception uninterruptedly from one month before, during and one month after treatment. She has been warned about the possibility of contraceptive failure.
5. Treatment should be started only on the 2nd or 3rd day of the next normal menstrual cycle.
6. A pregnancy test performed no more than 11 days before starting treatment must be negative. Monthly pregnancy tests are also strongly recommended during treatment.
7. Before starting treatment the doctor must provide patients of childbearing potential with detailed oral and written information on the danger of extremely severe malformations, on the precautions and on the risk incurred and possible consequences of the pregnancy occurring during treatment with isotretinoin or within one month after its completion.
8. Equally uninterrupted and effective contraception must be practiced in the event of retreatment, irrespective of the treatment-free interval, and must be continued for one month thereafter.
9. If the patient nevertheless becomes pregnant during treatment with isotretinoin or in the month following treatment, there is high risk of extremely severe fetal malformations (e.g. exencephaly). There is also an increased risk of spontaneous abortion.

The patient must fully understand the precautions and confirm her understanding and willingness to comply with the use of effective contraceptive methods that have been explained to her.
Two effective methods of contraception should be combined for this purpose.
Even women using no contraception because of preexisting infertility or sexual inactivity should be urged to follow the above guidelines for as long as they take isotretinoin.
To aid prescribers and patients in preventing fetal exposure to isotretinoin, the manufacturer provides contraceptive information designed to reinforce the warnings about the drugs teratogenecity and the mandatory use of reliable contraception in patients of childbearing age:

- Patient information brochure with a consent form for female patients.
- Brochure on contraception.
- Guidelines for physicians on use of a checklist when prescribing for women.

Female patients must be given the contraceptive information both orally and in writing.
The following extremely severe malformations have been reported in the children of mothers who have taken isotretinoin during pregnancy: hydrocephalus, microcephaly, deformity of the pinna of the ear (microtia), small or absent external auditory canal, *microphthalmia, cardiovascular malformations*, facial dysmorphism, abnormal thymus morphology, parathyroid hypofunction and cerebellar malformations.
If pregnancy occurs, the physician and patient should determine together whether it is advisable to continue the pregnancy.

COMPOSITION

Active Ingredients

SOTRET 10 mg
Each capsule contains
Isotretinoin Ph. Eur. 10 mg

SOTRET 20 mg
Each capsule contains
Isotretinoin Ph. Eur. 20 mg

Excipients
Hydrogenated Soyabean oil, hydrogenated vegetable oil, bees wax white, disodium edentate, butyl hydroxyl anisole, soyabean oil (refined), gelatin, glycerol, titanium dioxide, purified water.
Isopropyl alcohol & Paraffin light liquid*

Ferric Oxide Red (E172, CI No. 77491) - Shell colorant for Sotret 10 mg
Brilliant Blue FCF (E133, CI No. 42090) & Allura Red (E129, CI No. 16035) - Shell colorant for Sotret 20mg
* Processing aids

PHARMACEUTICAL FORM AND CONTENTS

Sotret Capsules 10mg & 20mg : Soft Gelatin Capsules packed in blister strips of 10's. Pack of 3x 10's in a carton.

THERAPEUTIC CLASS/ACTIVITY

SOTRET capsules contain the active ingredient isotretinoin, a retinoid. Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). The mechanism of action of isotretinoin has not been fully elucidated. However, it is clear that the clinical improvement seen in severe acne is paralleled by a dose dependent reduction in the activity of the sebaceous glands and a histologically confirmed decrese in their size. Isotretinoin has also been shown to have an anti inflammatory effect in the skin.

THERAPEUTIC INDICATIONS

SOTRET Capsules are indicated for severe forms of acne, especially nodulocystic acne and forms of acne with a tendency to scarring.

CONTRAINDICATIONS

SOTRET Capsules are contraindicated in pregnancy (in women who are pregnant or could become pregnant during treatment; see below), in nursing mothers, in liver failure, in preexisting hypervitaminosis A, in patients with markedly elevated blood lipid levels and in patients who are hypersensitive to this medication or to any of its components.

PRECAUTIONS

General
Although an effect of isotretinoin on bone loss is not established, physicians should use caution when prescribing isotretinoin to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.
Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on treatment with isotretinoin or following cessation of treatment with isotretinoin while involved in these activities. While causality to isotretinoin has not been established, an effect cannot be ruled out.
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.
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

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.

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 topical /injectable/ implantable/ insertable hormonal birth control products. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal 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.
Norethindrone/ethinyl estradiol: In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving Norethindrone/Ethinyl Estradiol Tablets as an oral contraceptive agent, isotretinoin at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
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. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and isotretinoin. Therefore, caution should be exercised when using these drugs together.
Systemic Corticosteroids: Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and isotretinoin. Therefore, caution should be exercised when using these drugs together.
Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. *Isotretinoin use is associated with depression in some patients* (see **WARNINGS and ADVERSE REACTIONS**). 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.

Carcinogenicity/Mutagenicity
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.

Use in Children
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**). Use of isotretinoin in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (≥18 years). Results from this study demonstrated that isotretinoin, at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.
In studies with 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 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 were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range 1.6% to -7.6%) in 5 of 8 patients (62.5%).
In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of 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**).

Use in Pregnancy and Lactation
Category X, see CONTRAINDICATIONS AND boxed WARNINGS.
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.

Use in Elderly
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**).

Effect on Driving/Machine operating ability
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.

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you . Follow strictly the doctors prescription , the method of use and the instructions of the pharmacist who sold the medicament.
The doctor and the pharmacist are the experts in medicines, their benefits and risks.
Do not by yourself interrupt the period of treatment prescribed.
Do not repeat the same prescription without consulting your doctor.
Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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**).
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**).
Glucose: Some patients receiving isotretinoin 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 postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

WARNINGS

Psychiatric Disorders
Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. 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**).
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**).
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 in excess of 800 mg/dL have been reported in patients treated with isotretinoin. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving isotretinoin in clinical trials. In addition, approximately 15% developed a decrease in highdensity 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.
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**).
The cardiovascular consequences of hypertriglyceridemia associated with isotretinoin are unknown.
Hearing Impairment
Impaired hearing has been reported in patients taking isotretinoin; 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 isotretinoin treatment and be referred for specialized care for further evaluation (see **ADVERSE REACTIONS**).
Hepatotoxicity
Clinical hepatitis considered to be possibly or probably related to isotretinoin 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 isotretinoin, the drug should be discontinued and the etiology further investigated.
Inflammatory Bowel Disease
Isotretinoin 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 isotretinoin treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue isotretinoin immediately (see **ADVERSE REACTIONS**).
Skeletal
Effects of multiple courses of isotretinoin 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 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 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 hipbone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range 1.6% to -7.6%) in 5 of 8 patients (62.5%).
In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of 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**).
Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin population. While causality to isotretinoin has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that isotretinoin 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. 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 isotretinoin treatment courses for acne are unknown.
In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of isotretinoin 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 isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown.
Vision Impairment
Visual problems should be carefully monitored. All isotretinoin patients experiencing visual difficulties should discontinue isotretinoin treatment and have an ophthalmological examination (see **ADVERSE REACTIONS**).
Corneal Opacities: Corneal opacities have occurred in patients receiving isotretinoin 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 have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug (see **ADVERSE REACTIONS**).

DOSAGE AND ADMINISTRATION

SOTRET Capsules should only be prescribed by doctors who are experienced in the use of systemic retinoids (preferably dermatologists) and clearly understand the risk of malformations if **SOTRET** is taken during pregnancy.
SOTRET capsules should be taken once or twice daily with meals.
The therapeutic response to **SOTRET** and its effects are dose dependent and not the same in all patients. Individual dose adjustments are therefore necessary during treatment. **SOTRET** therapy should be initiated at a dose of 0.5 mg/kg body weight daily. In most patients, the dose is between 0.5 and 1.0 mg/kg body weight daily. In patients with severe acne or truncal acne a higher dose of up to 2 mg/kg body weight may be needed.
A cumulative dose of 120 mg/kg body weight per treatment course was shown to increase remission rates and prevent recurrence. Treatment duration in a patient therefore varies with the daily dose employed. Complete remission of acne is often achieved with treatment duration of 16 to 24 weeks. Inpatients displaying symptoms of severe intolerance at the recommended dose, treatment should be continued at lower dose. Treatment will be longer as a result. In most patients, complete resolution of acne was achieved with a single treatment cycle. In the event of frank relapse, a repeat course of **SOTRET** can be administered at the same daily and cumulative treatment dose as before. Since further improvements in the acne can still be observed for up to 8 weeks after completing the treatment, repeat treatment should not be initiated until this period has not elapsed.

WITHDRAWAL EFFECTS, IF ANY

The termination of treatment with isotretinoin is unlikely to be associated with withdrawal effects; however, treatment should be discontinued only on the advice of the treating physician.

OVERDOSAGE and its Management

The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice (>600 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the rat dose for total body surface area and >300 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. All symptoms quickly resolved without apparent residual effects.
Isotretinoin causes serious birth defects at any dosage. 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. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling (see 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.
Missed dose instructions
In case a dose is missed, it should be taken as soon as possible unless it is almost time for the next dose. If several doses are missed, the pharmacist/physician must be informed.

ADVERSE REACTIONS

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 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
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.
Body as a Whole: allergic reactions, including vasculitis, systemic hypersensitivity, edema, fatigue, lymphadenopathy, weight loss.
Cardiovascular: palpitation, tachycardia, vascular thrombotic disease, stroke.
Endocrine/Metabolic: hypertriglyceridemia, alterations in blood sugar levels. *Gastrointestinal:* inflammatory bowel disease, hepatitis, pancreatitis, bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms.
Hematologic: allergic reactions, anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis.
Musculoskeletal: skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density, musculoskeletal symptoms (sometimes severe) including back pain and arthralgia, transient pain in the chest, arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis.
Neurological: 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, emotional instability.
Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.
Reproductive System: abnormal menses
Respiratory: bronchospasms (with or without a history of asthma), respiratory infection, voice alteration
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, pruritus,
pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, sweating, urticaria, vasculitis (including Wegener's granulomatosis), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting).
Special Senses
Hearing: hearing impairment, tinnitus.
Vision: corneal opacities, decreased night vision which may persist, cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances.
Urinary System: glomerulonephritis, nonspecific urogenital findings.
Laboratory
Elevation of plasma triglycerides, decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment.
Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH.
Elevation of fasting blood sugar, elevations of CPK, hyperuricemia.
Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis), elevated sedimentation rates, elevated platelet counts, thrombocytopenia.
White cells in the urine, proteinuria, microscopic or gross hematuria.

Expiry Date with Warning
The product should not be used after the expiry date mentioned on the pack.

STORAGE
Store below 25°C, protected from light.

SUPPLY
Sotret Capsules 10mg & 20mg - 3x10's blister strips in a carton.

SHELF LIFE
24 Months

Date of Last Revision of Package Leaflet
January 2005

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

MARKETING AUTHORIZATION HOLDER
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