For the use only of a Dermatologist

Isotretinoin Capsules USP

ISOTROIN

CONTRAINDICATIONS

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

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

- Must have severe disfiguring nodular acne that is recalcitrant to standard therapies (see INDICATIONS AND USAGE for definition)
- Must be capable of complying with the mandatory contraceptive measures required for Isotretinoin therapy and understand behaviours associated with an increased risk of pregnancy
- Must have had a negative urine or serum pregnancy test when the patient is qualified for Isotretinoin therapy by the prescriber, and must have had a second negative urine or serum pregnancy test on the second day of the next normal menstrual period or at least 11 days after the last unprotected act of sexual intercourse, whichever is later. Major human fetal abnormalities related to Isotretinoin administration have been documented: CNS abnormalities (including cerebral abnormalities, cerebellar malformation,hydrocephalus, microcephaly, cranial nerve deficit); skull abnormality; external ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); cardiovascular abnormalities; facial dysmorphia; cleft palate; thymus gland abnormality; parathyroid hormone deficiency. Effective contraception must be used for at least 1 month before beginning Isotretinoin therapy, during therapy, and for 1 month following discontinuation of therapy even where there has been a history of infertility, unless due to hysterectomy. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, even when one of the forms is a hormonal contraceptive method. If a pregnancy does occur during treatment, the prescriber and patient should discuss the desirability of continuing the pregnancy

AVOID PREGNANCY

COMPOSITION

Isotroin-10

Each soft gelatin capsule contains
Isotretinoin USP ..... 10 mg

Isotroin-20

Each soft gelatin capsule contains
Isotretinoin USP ..... 20 mg

DESCRIPTION

Isotretinoin is a retinoid, which inhibits sebaceous gland function and keratinization. The exact mechanism of action of Isotretinoin is unknown. 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 Isotretinoin, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

INDICATIONS

Cystic and conglobate acne, severe recalcitrant nodular acne: Isotroin 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, **Isotroin** should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, for female patients of childbearing potential, **Isotroin** is indicated only for those females who are not pregnant.

DOSAGE AND ADMINISTRATION

The recommended dosage range for **Isotroin** is 0.5 to 2 mg/kg given in 2 divided doses daily for 15 to 20 weeks. It is recommended that for most patients the initial dosage of Isotroin be 0.5 to 1 mg/kg/day. Patients whose disease is very severe or is primarily manifested on the trunk may require up to the maximum recommended dosage, 2 mg/kg/day. 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.

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. The optimal interval before re-treatment has not been defined for patients who have not completed skeletal growth.

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. Contraceptive measures must be followed for any subsequent course of therapy. Isotretinoin should be administered with food.

ISOTROIN DOSING BY BODY WEIGHT

Body Weight	Total mg/Day		
Kilograms	0.5 mg/kg	1 mg/kg	2 mg/kg
40	20	40	80
50	25	50	100
60	30	60	120
70	35	70	140
80	40	80	160
90	45	90	180
100	50	100	200

CONTRAINDICATIONS

Isotroin is contraindicated in patients who are hypersensitive to this medication or to any of its components. **Isotroin** should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsules.

Isotroin is contraindicated in pregnancy, hypervitaminosis A, hepatic and renal insufficiency, in patients with excessively elevated blood lipid values, and as supplementary treatment with tetracyclines.

WARNINGS AND PRECAUTIONS

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

Drug Interactions:

Vitamin A: Because of the relationship of Isotretinoin to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.

Tetracyclines: Concomitant treatment with Isotretinoin and tetracyclines should be avoided because Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.

Oral contraceptives: It is not known if hormonal contraceptives differ in their effectiveness when used with Isotretinoin. Therefore, it is critically important that women of childbearing potential use two effective forms of contraception simultaneously, unless absolute abstinence is the chosen method, even when one of the forms is a hormonal contraceptive method.

Laboratory Tests:

- ***Pregnancy Test:*** Female patients of childbearing potential must have negative results from two urine or serum pregnancy tests. The first test is to be performed when the patient is qualified for Isotroin therapy by her prescriber. The second test is to be performed on the second day of her next menstrual cycle or 11 days after her last unprotected act of sexual intercourse, whichever is later. Additional pregnancy tests are to be conducted monthly during treatment.
- ***Lipids:*** Pretreatment and follow-up blood lipids should be obtained under fasting conditions. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to **Isotroin** is established.
- ***Liver Function Tests:*** Pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to **Isotroin** has been established.

Psychiatric Disorders: Isotroin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Isotretinoin therapy may be insufficient; further evaluation may be necessary.

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 **Isotroin** immediately and be referred to a neurologist for further diagnosis and care.

Pancreatitis: Acute pancreatitis has been reported in patients with either elevated or normal serum triglycerides levels. **Isotroin** should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Lipids: Elevations of serum triglycerides have been reported in patients treated with Isotretinoin.

Decrease in high-density lipoproteins and increase in cholesterol levels have also been reported. Some patients have been able to reverse triglycerides 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 **Isotroin** is given and then at intervals until the lipid response to **Isotroin** 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 **Isotroin** therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If **Isotroin** therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended. The cardiovascular consequences of hypertriglyceridemia associated with Isotretinoin are unknown.

Hearing Impairment: Patients who experience tinnitus or hearing impairment should discontinue **Isotroin** treatment and be referred to specialized care for further evaluation.

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, some of which normalize 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. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue **Isotroin** immediately.

Skeletal Hyperostosis: 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.

Premature Epiphyseal Closure: There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses, but a causal relationship is not known.

Decreased Night Vision: Visual problems should be carefully monitored. All **Isotroin** patients experiencing visual difficulties should discontinue **Isotroin** treatment and have an ophthalmological examination. Because of the onset of decreased night vision in some patients, patients should be warned to be cautious when driving or operating any vehicle at night.

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.

Carcinogenesis, Mutagenesis and Impairment of Fertility: The relevance of the clinical findings of animal studies in humans is uncertain. With Isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

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 **Isotroin.**

ADVERSE REACTIONS

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, colitis, ileitis, nausea, other nonspecific gastrointestinal symptoms.

Hematologic: Anaemia, thrombocytopenia, neutropenia.

Musculoskeletal: Skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, mild to moderate musculoskeletal symptoms including arthralgia, elevations of CPK, arthritis, tendonitis, other types of bone abnormalities

Neurological: Pseudotumor cerebri, dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope.

Psychiatric: Suicidal ideation, suicide attempts, suicide, depression, psychosis, emotional instability.

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, nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, (including Wegener's granulomatosis;), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting.

Special Senses: Hearing impairment, tinnitus, corneal opacities, decreased night vision, 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.

OVERDOSAGE:

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.

STORAGE: Store below 30°C. Protect from light

PRESENTATION:

Isotroin-10 .... Blister Pack of 10 capsules
Isotroin-20 .... Blister Pack of 10 capsules

PATIENT INFORMATION LEAFLET

WHAT IS ISOTROIN ?

ISOTROIN contains Isotretinoin and is prescribed to treat severe form of pimples which in medical terminology is called as severe refractory nodulocystic acne.

WHAT FACTS DO I NEED TO KNOW ABOUT ISOTROIN ?

- **ISOTROIN** is indicated in severe pimples in both, males and females and is to be taken **under doctor's supervision only.**
- **ISOTROIN** is strictly a prescription based drug. Under no circumstances you should suggest it to anyone else even if his or her condition resembles yours.
- You might have difficulty in using contact lenses.
- Vitamin A supplements should be avoided while on therapy.
- Patients with family or personal history of diabetes, liver disease, heart disease or depression should inform their doctor before the start of the therapy.
- If your acne returns do not take **ISOTROIN** of your own on your old prescription.Consult your doctor again.

WHAT PRECAUTIONS DO I NEED TO TAKE WHEN I AM ON ISOTROIN THERAPY ?

- Do not donate blood during the course of therapy and 1 month after discontinuation of therapy.
- Avoid prolonged exposure to sunlight.Use sunscreen.
- Avoid night driving.
- Avoid removal of hair by using wax due to the increased chances of scarring and for at least 6 months thereafter.

Special precautions to be taken **by female patients of childbearing potential** :

- Patients should not be pregnant before starting this medication.
- Patients should use effective contraceptive methods one month prior to starting the therapy, during the therapy and one month after stopping the therapy.
- Avoid breastfeeding.

*Female patients are required to sign a consent form prior to starting **ISOTROIN** therapy.*

FOR MORE INFORMATION ON THE ABOVE PLEASE CONTACT YOUR DOCTOR.

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