ISOTROIN Capsules (Isotretinoin)
To be sold by retail on the prescription of a Dermatologist only

Black Box Warnings

Isotretinoin may cause severe birth defects; female patients must not take this medicine if they are pregnant or may likely become pregnant during treatment. Pregnancy should be avoided for 6 months after stopping the treatment. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. Potentially any foetus exposed during pregnancy can be affected. Presently, there are no accurate means of determining whether an exposed fetus has been affected.

Birth defects that have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system (CNS), 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 anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain abnormalities previously noted.

If pregnancy does occur during the treatment of a female patient who is taking ISOTROIN, ISOTROIN must be discontinued immediately and she should be referred to an obstetrician-gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Qualitative And Quantitative Composition

ISOTROIN-10 Capsules
Each soft gelatin capsule contains:
Isotretinoin IP (10 mg)
Approved colour used in capsule shell (-)

ISOTROIN-20 Capsules
Each soft gelatin capsule contains:
Isotretinoin IP (20 mg)
Approved colour used in capsule shell (-)

Dosage Form(S) And Strength(S)
Soft gelatin capsule contains Isotretinoin 10 mg/20 mg

### Clinical Particulars

#### Therapeutic Indications

Cystic and conglobate acne, severe nodular acne unresponsive to antibiotic therapy

#### Posology and Method of Administration

Patients must sign a consent form before undertaking the treatment of ISOTROIN. The required laboratory testing must be completed prior to dosing ISOTROIN. Pregnancy Testing and Contraceptive measures must be followed prior to dosing ISOTROIN. ISOTROIN should be administered with a meal.

The recommended dosage range for ISOTROIN 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 1.0 mg/kg/day, it was found that all dosages provided initial clearing of disease, but there was a greater need for re-treatment 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 ISOTROIN 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 isotretinoin has not been established. Once-daily dosing is not recommended.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After an off-therapy period of 2 months or more, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before re-treatment has not been defined for patients who have not completed skeletal growth.

Long-term use of isotretinoin, even in low doses, has not been studied, and is not recommended. It is important that ISOTROIN be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of isotretinoin on bone loss is unknown.

Contraceptive measures must be followed for any subsequent course of therapy.

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Total mg/day</th>
</tr>
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<tbody>
<tr>
<td>Kilograms</td>
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<tr>
<td>Pounds</td>
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<tr>
<td>40</td>
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* See DOSAGE AND ADMINISTRATION: the recommended dosage range is 0.5 to 1.0 mg/kg/day.
Special Population

Patients with Renal Impairment
In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose.

Paediatric population
Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age due to a lack of data on efficacy and safety.

Patients with Intolerance
In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

Laboratory Testing

Pregnancy Testing

Liver Function Test
Perform liver function tests prior to use of ISOTROIN.

Contraindications

Pregnancy
Pregnancy Category X
See BLACK BOX WARNINGS.

Allergic Reactions
ISOTROIN are 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 the parabens, which are used as preservatives in the gelatin capsules.

Special Warnings and Precautions for Use

ISOTROIN may cause severe birth defects; female patients must not take this medicine if they are pregnant or may likely become pregnant during treatment. Pregnancy should be avoided for 6 months after stopping the treatment. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ISOTROIN in any amount, even for short periods of time.

Embryofetal Toxicity

Teratogenicity
Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin. Patients who can become pregnant must comply with the pregnancy testing and contraception requirements. There are no accurate means of determining whether an exposed fetus has been affected.
No Blood Donation
Patients must be informed not to donate blood during isotretinoin therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant patient whose fetus must not be exposed to isotretinoin.

Hypersensitivity
Anaphylactic reactions, and other allergic reactions have been reported in isotretinoin-treated patients. 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: Females of reproductive potential must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin. The second pregnancy test (a confirmation test) must be done in a laboratory. The interval between the two tests must be at least 19 days.

For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 methods of contraception for one month.

For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 methods of contraception for one month.

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

Lipids: Pre-treatment 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 ISOTROIN is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin.

Liver Function Tests: Pre-treatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to ISOTROIN has been established. Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported in patients on isotretinoin, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to isotretinoin has been established.

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 an isotretinoin clinical trial of 24 patients, marked elevations in CPK (≥350 U/L) were observed in approximately 24% of patients. In another clinical trial of 217 pediatric patients (12 – 17 years) 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 clinical trial.

**Psychiatric Disorders**

Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviours. No mechanism of action has been established for these events (see UNDESIRABLE EFFECTS, Psychiatric). Prior to initiation of ISOTROIN 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 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 ISOTROIN 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 isotretinoin 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 ISOTROIN therapy is appropriate in this setting; for some patients, the risks may outweigh the benefits of ISOTROIN therapy.

**Pseudotumour cerebri**

Isotretinoin use has been associated with a number of cases of pseudotumour 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 pseudotumour 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 ISOTROIN immediately and be referred to a neurologist for further diagnosis and care.

**Serious Skin Reactions**

There have been post marketing reports of erythema multiforme and severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) associated with isotretinoin use. These events may be serious and result in death, life-threatening events, hospitalization or disability. Patients should be monitored closely for severe skin reactions and discontinuation of ISOTROIN should be considered if warranted.

**Pancreatitis**

Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. ISOTROIN should be stopped if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur. In rare instances, fatal haemorrhagic pancreatitis has been reported.

**Lipid Abnormalities**

Elevations of serum triglycerides have been reported 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 high density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects of 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 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 of triglyceridemia 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 hypertriglyceridaemia 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 reaction have not been established. Patients who experience tinnitus or hearing impairment should discontinue ISOTROIN treatment and be referred for 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, in approximately 15% of individuals treated during clinical trials with isotretinoin, 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 aetiology 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 diarrhoea should discontinue ISOTROIN immediately.

Skeletal Abnormalities
Bone Mineral Density
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. Long-term effects have not been studied. It is important that ISOTROIN be given at the recommended doses for no longer than the recommended duration.

Hyperostosis
Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed on X-rays 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 of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown.

Vision Impairment
Visual problems should be carefully monitored. All ISOTROIN patients experiencing visual difficulties should discontinue ISOTROIN treatment and have an ophthalmological examination.

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.

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.

Dry Eye

Dry eye has been reported in subjects during isotretinoin therapy. Patients who wear contact lenses may have trouble wearing them while on isotretinoin treatment and afterwards.

Drug Interactions

**Vitamin A:** Isotretinoin is closely related to vitamin A. Therefore, the use of both vitamin A and isotretinoin at the same time may lead to vitamin A side effects. 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.

**Micro-dosed progesterone preparations:** Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during isotretinoin therapy.

**Norethindrone/ethinyl estradiol:** In a trial of 31 premenopausal female patients with severe recalcitrant nodular acne receiving Norethindrone/ethinyl estradiol 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). 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.

**St John's wort:** Isotretinoin use is associated with depression in some patients. (see Psychiatric Disorders and Undesirable Effects, *Psychiatric*). Patients should be prospectively cautioned not to self-medicate with the herbal supplement, St John's wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St John's wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St John's wort.

**Phenytoin:** Isotretinoin has not been shown to alter the pharmacokinetics of phenytoin in a study in 7 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. Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.

Use in Special Population

**Pregnant Women**

Pregnancy Category X
See BLACK BOX WARNINGS.

**Lactating Women**

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.

**Paediatric Patients**

The use of isotretinoin in paediatric patients less than 12 years of age has not been studied. The use of ISOTROIN for the treatment of severe recalcitrant nodular acne in paediatric patients aged 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists.

**Geriatric Patients**

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.

**Effects on Ability to Drive and Use Machines**

Isotretinoin could potentially have an influence on the ability to drive and use machines. A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy. 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 machines. Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

**Undesirable Effects**

Clinical Trials and Postmarketing Surveillance
The adverse reactions listed below reflect 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 hypertriglyceridaemia are usually dose-related. Most adverse reactions reported in clinical trials with isotretinoin were reversible when therapy was discontinued; however, some persisted after cessation of therapy.

**Body as a Whole:** Allergic reactions, including vasculitis, anaphylactic reactions, systemic hypersensitivity, oedema, fatigue, lymphadenopathy, weight loss.

**Infections:** Gram positive (mucocutaneous) bacterial infection

**Cardiovascular:** Palpitation, tachycardia, vascular thrombotic disease, stroke.

**Endocrine/Metabolic/Nutrition disorders:** decreased appetite, weight fluctuation, hyperlipidaemia. Hypertriglyceridaemia, alterations in blood sugar levels, hyperuricaemia.

**Gastrointestinal:** Nausea, constipation, diarrhea, abdominal pain, vomiting, inflammatory bowel disease, hepatitis, pancreatitis, bleeding and inflammation of the gums, colitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea, oesophagitis/oesophageal ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms.

**Haematologic:** Allergic reactions, anaemia, thrombocytopenia, neutropenia, red blood cell sedimentation rate increased, thrombocytosis, rare reports of agranulocytosis.
Infections and Infestations: nasopharyngitis, hordeolum, upper respiratory tract infection

Musculoskeletal and Connective Tissue: Skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density, musculoskeletal symptoms (sometimes severe), including back pain (particularly in children and adolescent patients), myalgia and arthralgia, transient pain in the chest, arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis. musculoskeletal discomfort, musculoskeletal pain, neck pain, pain in extremity, musculoskeletal stiffness

Neurological: Pseudotumour cerebri, dizziness, drowsiness, headache, lethargy, malaise, nervousness, paraesthesias, seizures, convulsions, stroke, syncope, weakness, benign intracranial hypertension

Psychiatric: Suicidal ideation, insomnia, suicide attempts, suicide, depression, irritability, panic attack, anger, euphoria, depression aggravated, psychosis, aggression, violent behaviours, anxiety, mood alterations, abnormal behaviour, emotional instability, Aggressive tendencies, Depression including aggravation of pre-existing depression. 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, Sexual dysfunction including erectile dysfunction and decreased libido

Respiratory: Bronchospasms (with or without a history of asthma), respiratory infection, voice alteration, epistaxis, nasal dryness, nasopharyngitis, Bronchospasm (particularly in patients with asthma), Hoarseness

Skin and Appendages: Acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, dermatitis, localised exfoliation, epistaxis, eruptive xanthomas, erythema multiforme, 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, seborrhoea and eczema), Stevens-Johnson syndrome, sunburn susceptibility increased, sweating, toxic epidermal necrolysis, urticaria, vasculitis (including Wegener’s granulomatosis) abnormal wound healing (delayed healing or exuberant granulation tissue with crusting).

Special Senses

Hearing: Hearing impairment, tinnitus.

Vision: eye pruritis, asthenopia, ocular hyperemia, increased lacrimation, Corneal opacities, decreased night vision which may persist, cataracts, colour vision disorder, conjunctivitis, blepharitis, eye irritation, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances, blurred vision, contact lens intolerance, papilloedema (as sign of benign intracranial hypertension).

Urinary System: Glomerulonephritis, nonspecific urogenital findings.

Laboratory:
Elevation of plasma triglycerides, decrease in serum high-density lipoprotein levels, elevations of serum cholesterol during treatment.
Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH, blood alkaline phosphatase increased, blood bilirubin increased,
Elevation of fasting blood sugar, elevations of CPK and hyperuricaemia.
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 and thrombocytopenia.
White cells in the urine, proteinuria, microscopic or gross haematuria.
Increase blood creatinine phosphokinase Bone mineral density decreased.
If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

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 (see BLACK BOX WARNINGS).

Patients who can become pregnant who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counselling about the risks to the fetus. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counselling. 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 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.

Pharmacological Properties

Mechanism of Action

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

Pharmacodynamic Properties

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 ISOTROIN, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

Pharmacokinetic Properties

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. The time to peak concentration ($T_{\text{max}}$) was also increased with food and may be related to a longer absorption phase. Therefore, ISOTROIN should always be taken with food. 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.

Distribution

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

Metabolism

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

After a single 80 mg oral dose of isotretinoin to 74 healthy adult subjects, concurrent administration of food
increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions. All of these metabolites possess retinoid activity that is in some in vitro models more than that of the parent isotretinoin. 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 the steady state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

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

**Elimination**

Following oral administration of an 80 mg dose of $^{14}$C-isotretinoin as a liquid suspension, $^{14}$C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the faeces 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 fasted conditions, the mean ± S.D. elimination half-lives ($T_{1/2}$) of isotretinoin and 4-oxo-isotretinoin under fasted states were 18 hours and 38 hours, respectively. 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 0.90 to 5.43 in patients with cystic acne.

**Special Population**

**Paediatric** The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 paediatric patients (aged 12 to 15 years) and 19 adult patients (≥18 years) who received isotretinoin for the treatment of severe recalcitrant nodular acne. In both age groups, 4-oxo-isotretinoin was the major metabolite; tretinoin and 4-oxo-tretinoin were also observed.

The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses in paediatric patients are summarized in Table 2. There were no statistically significant differences in the pharmacokinetics of isotretinoin between paediatric and adult patients.

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<th>Parameter</th>
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<td>$T_{1/2}$ (hr)</td>
<td>-</td>
<td>15.69 (5.12)</td>
</tr>
</tbody>
</table>

* The single and multiple dose data in this table were obtained following a non-standardized meal that is not comparable to the high-fat meal. ** Median (range)
In paediatric patients (aged 12 to 15 years), the mean ± S.D. elimination half-lives ($t_{1/2}$) of isotretinoin and 4-oxo-isotretinoin were 15.7 ± 5.1 hours and 23.1 ± 5.7 hours, respectively. The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 for paediatric patients.

### Nonclinical Properties

#### Animal Toxicology or Pharmacology

**Acute Toxicity**
The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

**Chronic Toxicity**
A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin. All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1-2 weeks.

**Teratogenicity**
Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age.

**Mutagenicity**
Isotretinoin has not been shown to be mutagenic nor carcinogenic in *in vitro* or *in vivo* animal tests respectively.

### Description

ISOTROIN contains 10 mg or 20 mg of isotretinoin (a retinoid) in soft gelatin capsules for oral administration.

### Pharmaceutical Particulars

#### Not applicable.

#### Shelf-life

As on the pack

#### Packaging Information

ISOTROIN-10: Blister pack of 10 capsules
ISOTROIN-20: Blister pack of 10 capsules

#### Storage and Handling Instructions
Store in a cool dry place.
Protect from light.

Patient Counselling Information

What are ISOTROIN?
ISOTROIN contains isotretinoin and are 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 are indicated in severe pimples in both males and females and is to be taken under a doctor's supervision only.
ISOTROIN are strictly a prescription-based drug. Under no circumstances should you 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 a 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 a sunscreen.
Avoid night driving.
Avoid removal of body hair by using wax due to the increased chances of scarring and for at least 6 months thereafter.

What special precautions to be taken by female patients of childbearing potential?
ISOTROIN may cause severe birth defects; you must not take this medicine if you are pregnant or may likely become pregnant during treatment.
You should also avoid pregnancy for 6 months after stopping the treatment.
Patients should use effective contraceptive methods 1 month prior to starting the therapy, during the therapy, and 6 months after stopping the therapy.
Avoid breastfeeding during the therapy and one month after stopping the therapy.
You must sign a consent form before undertaking the treatment of isotretinoin.

Details Of Manufacturer

D 7, MIDC, Industrial Area,
Kurkumbh, Tal – Daund
Dist – Pune 413802.

Details Of Permission Or Licence Number With Date

License No: 28-PD/42
Issue Date: 18/02/2017

Date Of Revision

29/11/2019
ISOTROIN Capsules

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