PRESCRIBING INFORMATION:

For the use of Registered Medical Practitioner or a Hospital or a Laboratory only.

TRETIVA - 5/10/20/25/30/40

(Isotretinoin capsules IP 5/10/20/25/30/40 mg)

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

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

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

Documented external abnormalities include: skull abnormality; ear abnormalities (including 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 of the abnormalities previously noted.

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

COMPOSITION

TRETIVA-5
Each Soft gelatin capsule contains:
Isotretinoin IP.....5 mg
Excipients..... q.s.

TRETIVA-10
Each Soft gelatin capsule contains:
Isotretinoin IP.....10 mg
Excipients..... q.s.

TRETIVA-20
Each Soft gelatin capsule contains:
Isotretinoin IP.....20 mg
Excipients..... q.s.

TRETIVA-25
Each Soft gelatin capsule contains:
Isotretinoin IP.....25 mg
Excipients..... q.s.

TRETIVA-30
Each Soft gelatin capsule contains:
Isotretinoin IP.....30 mg
Excipients..... q.s.

TRETIVA-40
Each Soft gelatin capsule contains:
Isotretinoin IP.....40 mg
Excipients..... q.s.

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 as a result of 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. Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A).

CLINICAL PHARMACOLOGY

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. Clinical improvement in nodular acne patients occurs as a result of a reduction in sebum secretion.

Pharmacokinetics

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. Both peak plasma concentration (C_{max}) and the total exposure (AUC) of isotretinoin increases following a standardized high-fat meal when compared with isotretinoin given under fasted conditions. The observed elimination half-life remains unchanged. Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

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). All of these metabolites possess retinoid activity more than the parent Isotretinoin. After multiple oral dose administration of Isotretinoin to adult cystic acne patients (≥18 years), the exposure of patients to 4-*oxo* isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of Isotretinoin. Invitro studies indicate that the primary CYP_{450} isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4 and 2B6. 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 excreted in the feces and urine in relatively equal amounts (total of 65% to 83%).After a single 80 mg oral dose of isotretinoin to 74 healthy adult subjects under fed conditions, elimination half-lives ($t_{1/2}$) of isotretinoin was 21.0 ± 8.2 hours.

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (≥18 years). There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.In pediatric patients (12 to 15 years), the mean ± SD 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 pediatric patients.

INDICATIONS

Cystic and conglobate acne, severe recalcitrant nodular acne: Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5mm 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, Isotretinoin 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, Isotretinoin is indicated only for those females who are not pregnant.

DOSAGE AND ADMINISTRAITON

The recommended dosage range for Isotretinoin is 0.5 to 1 mg/kg given in 2 divided doses daily for 15 to 20 weeks. It is recommended that for most patients the initial dosage of Isotretinoin be 0.5 to 1 mg/kg/day. Adult 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. Long-term use of Isotretinoin in low doses is not recommended. It is important that Isotretinoin be given at the recommended doses for no longer than the recommended duration. Isotretinoin should be administered with food.

Isotretinoin Dosing by Body Weight (Based on Administration With Food)

Body Weight		Total mg/day		
Kilograms	Pounds	0.5 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

*The recommended dosage range is 0.5 to 1.0 mg/kg/day.

CONTRAINDICATIONS

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

Pregnancy Category X. **(See Boxed CONTRAINDICATIONS AND WARNINGS).**

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

Must NOT be pregnant or breast feeding. Must be reliable in understanding and carrying out instructions. Must be capable of complying with the mandatory contraceptive measures required for isotretinoin therapy and understand behaviors associated with an increased risk of pregnancy.

WARNING AND PRECAUTIONS

Females who are pregnant must not use isotretinoin. 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. Female patients should use 2 forms of effective contraception 1 month before starting isotretinoin, while taking isotretinoin, and for 1 month after isotretinoin has been stopped. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another isotretinoin prescription is written.

Hypersensitivity: Anaphylactic reaction, 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.

Psychiatric Disorders: Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. No mechanism of action has been established for these events. Prior to initiation of isotretinoin 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. 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 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.

Pancreatitis: Acute pancreatitis has been reported in patients with either elevated or normal serum triglycerides levels. Isotretinoin 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. Decreases 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 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. The cardiovascular consequences of hypertriglyceridemia associated with Isotretinoin are unknown.

Hearing Impairment: Patients who experience tinnitus or hearing impairment should discontinue Isotretinoin 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 Isotretinoin immediately.

Bone Mineral Density: 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. Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the isotretinoin receiving patients. Hence it is important that isotretinoin be given at the recommended doses for no longer than the recommended duration.physicians should use caution when prescribing isotretinoin to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia etc.

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 course 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 Isotretinoin patients experiencing visual difficulties should discontinue Isotretinoin 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 dosage 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 of were resolving at follow-up 6 to 7 weeks after discontinuation of the drug.

Patients should be informed that they must not share isotretinoin with anyone else because of the risk of birth defects and other serious adverse events.

Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to isotretinoin.

Patients should be reminded to take isotretinoin with a meal. To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.

Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy. Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during isotretinoin therapy and for at least 6 months thereafter due to the possibility of scarring.

Patients should be advised to avoid prolonged exposure to UV rays or sunlight. Neutropenia and rare cases of agranulocytosis have been reported. Isotretinoin should be discontinued if clinically significant decreases in white cell counts occur.

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 Isotretinoin 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 Isotretinoin is established.
- **Liver Function Tests**: Pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Isotretinoin has been established.

DRUG INTERACTIONS

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

Phenytoin: Isotretinoin has not been shown to alter the pharmacokinetics of phenytoin but 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.

Carcinogenesis, Mutagenesis and Impairment of Fertility: The relevance of the clinical findings of animal studies in humans is uncertain. Isotretinoin was not found to be mutagenic in a series of tests or assays. 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 Isotretinoin.

Pediatric Use

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

Geriatric Use

Effects of aging might be expected to increase some risks associated in elder patients with Isotretinoin therapy. Clinical studies showing no difference in response between younger and geriatric patients with Isotretinoin therapy.

ADVERSE REACTIONS

Cheilitis and hypertriglyceridemia are the most common side effects observed and were usually dose related.

Body as a Whole: Allergic reactions, including vasculities, 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, esophagitis/esophageal ulceration and other nonspecific gastrointestinal symptoms.

Hematologic: Anaemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis

Musculoskeletal: Skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, mild to moderate musculoskeletal symptoms including back pain, transient pain in the chest, 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, weakness.

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

Reproductive System: Abnormal menses.

Respiratory: Bronchospasm (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, hirsuitism, 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 tests: Elevation of plasma triglycerides, decrease in serum high-density lipoprotein (HDL) levels, elevation of serum cholesterol during treatment. Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH, elevation of fasting blood sugar, elevations of CPK, hyperuricemia. Decrease 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. Female patients of childbearing potential should have a pregnancy test at time of overdose and 1 month later; if positive, teratogenic risk should be discussed. 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.

STORAGE

Store below 25°C. Protect from light.

Patient Information Leaflet

1.What is TRETIVA ?

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

2.What facts do I need to know about TRETIVA?

- It is indicated in severe pimples in both, males and females and is to be taken under doctor's supervision only.
- It 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.Inform to your doctor if you are taking other medicines.
- 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 TRETIVA of your own on your old prescription.Consult your doctor again.

3.What special precautions to be taken by female patients of childbearing potential ?

- Patients should not be pregnant before starting this medication.It can cause severe birth defects in babies of women who take it while they are pregnant,
- 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.

4.What precautions do I need to take when I am on tretinoin therapy ?

- Do not donate blood during the course of therapy and 1 month after discontinuation of therapy.
- Do not have cosmetic procedures to smooth your skin, including waxing, or laser procedures, while you are using TRETIVA and for at least 6 months after you stop.
- Do not use birth control pills that do not contain estrogen ("minipills"). They may not work while you take TRETIVA
- Avoid prolonged exposure to sunlight. Use sunscreen.
- Avoid night driving.

PRESENTATION

TRETIVA-5/10/20/25/30/40 are available in strips of 10 capsules.

Manufactured by: Olive Healthcare
197/2, Athiyawad, Dabhel Village, Nani Daman (U.T.)
Daman – 396 210.

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INTAS
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