Treat A-20
Isotretinoin Soft Gelatin Capsules USP 20 mg

COMPOSITION:
Each Soft Gelatin Capsule Contains:
Isotretinoin USP 20 mg
Excipient q.s.
Approved colour used in soft gelatin capsule shell.

DESCRIPTION:
Treat A-20 contains Isotretinoin as an active ingredient.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Retinoid for treatment of acne.
ATC code: D10BA01
Mechanism of action
Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.
Pharmacokinetic Properties:
Absorption
The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability.
When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.
Distribution
Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9%).
The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.
Biotransformation
After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (alltrans retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxoisotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites include glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound.
Isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerisation.
Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man. In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo- isotretinoin and tretinoin.
No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.
Elimination
After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces.
Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours. Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy

THERAPEUTIC INDICATIONS:
Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.
POSOLOGY AND METHOD OF ADMINISTRATION:
Posology
Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.
The capsules should be taken with food once or twice daily.
Adults including adolescents and the elderly:
Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy.
For most patients, the dose ranges from 0.5-1.0 mg/kg per day.
Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial
additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-
24 weeks is normally sufficient to achieve remission.
In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose.
As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.
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 should not be used for the treatment of prepubertal acne and is not recommended in children 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.
Method of administration
For oral use.

CONTRAINDICATION:
Isotretinoin is contraindicated in women who are pregnant or breastfeeding.
Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.
Isotretinoin is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients Used in formulation.
Isotretinoin 20 mg Capsules contain soya oil and partially hydrogenated soya oil. Therefore, Isotretinoin 20 mg capsules are contraindicated in patients allergic to peanut or soya.
Isotretinoin is also contraindicated in patients.
- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A

SPECIAL WARNING AND PRECAUTION FOR USE:
Contraception
Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.
Male patients
The available data suggest that the level of maternal exposure from the semen of the patients receiving isotretinoin, is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin. Male patients should be reminded that they must not share their medication with anyone, particularly not females.
Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.
Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.
Psychiatric disorders
Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin.
Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.
Skin and subcutaneous tissue disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.
Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.
Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping
Allergic reactions
Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently.
Eye disorders
Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Cases of dry eyes not resolving after discontinuation of therapy have been reported. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.
Hepatobiliary disorders
Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.
Renal insufficiency
Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose.

DRUG INTERACTIONS:
Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.
Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided.
Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase

PREGNANCY AND BREAST-FEEDING
Pregnancy
The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.
If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology.
Breast-feeding
Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mother's milk, isotretinoin is contraindicated during breast-feeding.
Fertility
Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin

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.

UNDESIRABLE EFFECTS:
Blood and lymphatic system disorders:
Very Common
Thrombocytopenia, anaemia, thrombocytosis, red blood cell sedimentation rate increased
Common
Neutropenia
Eye disorders
Very Common
Blepharitis, conjunctivitis, dry eye, eye irritation
Respiratory, thoracic and mediastinal disorders:
Common
Nasopharyngitis, Bepistaxis, nasal dryness
Skin and subcutaneous tissues disorders:
Common
Pruritus, rash, erythematous, dermatitis, cheilitis, dry skin, localised exfoliation, skin
fragility (risk of frictional trauma)
Musculo-skeletal and connective tissue disorders:
Common
Arthralgia, myalgia, back pain (particularly in children and adolescent patients)

OVERDOSAGE:
Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment

SHELF LIFE:
36 Months

PACKAGING:
10 softgels are packed in Alu-PVC blister & such 3 blister is packed in printed carton along with pack insert

STORAGE CONDITION:
Stored at a temperature not exceeding 25°C. Protect from light and moisture.
Keep the medicine out of reach of children.

MANUFACTURED IN INDIA BY :
DR. SMITHS BIOTECH PVT. LTD.
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