Accutane ایکوٹین

(Isotretinoin U.S.P) آئیسوٹریٹینون (یو ایس پی)

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

RETINOID FOR SYSTEMIC TREATMENT OF ACNE.

1.2 TYPE OF DOSAGE

CAPSULES: 20mg

1.2 ROUTE OF ADMINISTRATION

oral.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Accutane is indicated for the treatment of severe forms of acne (nodular or oonglobate acne, or acne at nsk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy.

2.2 Dosage and Administration

Standard Dosage

Acoutane should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the nsk of teratogenicity associated with isotrentinoin therapy. Both female and male patients should be given a copy of the Patient Information Brochure (see sections 2.5 Use in Special Populations and 2.4 Warnings and Precautions).

The therapeutic response to Accutane and its adverse events are dose related and vary between patients. This necessitates individual dosage adjustment during therapy. Accutane therapy should be started at a dose of 0.5 mg/kg daily. For most patients the dose ranges from 0.5-1.0 mg/kg per day. Patients with very severe disease or with truncal acne may require higher daily doses up to 2.0 mg/kg.

The capsules should betaken with food once or twice daily.

A cumulative treatment dose of 120-150 mg/kg per treatment has been documented to increase remission rates and prevent relapse. The therrapy duration in individual patients therefore varies as a function of the daily dose. Complete remission of the acne is often achieved by a therapy course of 16-24 weeks. In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of a longer therapy duration.

In the majority of patients complete clearing of the acne is obtained with a single treatment course. In case of a definite relapse, a renewed course of Accutane therapy should be given with the same daily dose and cumulative treatment dose as previously since further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, retreatment should not be initiated until after this period.

2.21 Special Dosage Instructions

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 (see section 2.5.4Renal impairment).

2.3 Contraindication

Accutane is contraindicated

Women of child-bearing potential

Women of child-bearing potential unless the female patient meets all the conditions of the Pregnancy Prevention Programme (see section 2.4 Wamings and Precautions).

P regnant or breastfeeding women

Accutane is contraindicated in women who are pregnant or breastfeeding(see section 2.5 Use in Special Populations).

Telracyclines

Patients receiving concomitant treatment with tetracyclines (see section 2.4 Wamings and Precautions).

Hepatic insufficiency

Hepatic insufficiency (see section 2.4 Wamings and Precautions).

Hypervitaminosis A

Patients with pre-existing hypenritaminosis A (see section 2.6 Undesirable Effects).

Elevated blood lipid values

Patients with excessively elevated blood lipid values (see section 2.4 Warnings and Precautions).

Hypersensitivity

Accutane is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the occupants. Accutane contains soya oil, partially hydrogenated soya oil, and hydrogenated soya oil. Therefore, Accutane is contraindicated in patients allergic to soya.

2.4 Wernings and Precations

2.4.1 General

Accutane is TERATOGENIC.

There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral Accutane in any amount even for short periods. Potentially all exposed fetuses Can be affected.

Accutane is contraindicated in women of childbearing potential unless the female patient meets all the conditions of the Pregnancy Prevention Programme.

The pregnancy prevention information should be gtyen to the patients both orally and in writing.

Pregnancy Prevention Programme

The female patient must ensure that :

She understands the teratogenic risk.

She is reliable in understanding and carrying out instructions.

She must be informed by her physician of the hazards of becoming pregnant during and 1 month after treatment withAccutane.

She understands and accepts the need for effective contraception without any interruption for 1 month before beginning Accutane therapy, during therapy and for 1 month following dfficontinuation of therapy. At least 1, and preferably 2, complementary forms of contraception including a barrio method should be used

She must have a negative molt from a reliable pregnancytest within 11 days prior to the start of therapy. She must accept to undergo pregnancy testing during and 5 weeks after the end of treatment.

She must start Accutane therapy only on the 2nd or 3rd day of the next normal menstrual period.

She must be wamed of the possibility of contraception failure.

She understands the need for rigorous follow-up on a monthly basis.

She is informed and understands the potential consequences of pregnancy and the need to rapidly consuft if there is a nsk of pregnancy

Even if she has amenorthea she most follow all of the advice on effective contraception.

In the event of relapse treatment she must also use the same uninterrupted and effective contraceptive measures 1 month odor to, during, and for 1 month after Accutane therapy and the same reliable pregnancy evaluations should be followed.

She must fully understand the precautions and confirm her willingness to comply with reliable contraceptive measures as explained to her

She must use and be capable of complying with the mandatory effective contraceptive measures.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity must be advised to use effective contraceptive measures while taking Accutane, following the above guidelines.

The prescriber must ensure that:

The patients must have severe 'mesa(acne (nodular or conglobate acne, or acne at risk of permanent scarring) and acne which has failed to respond to standard therapies with systemic antibacterials and topical therapy.

Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment.

The dates and results of pregnancy tests should be documented.

The patient has used at least one and preferably two methods of effective contraception including a banter method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment

The patient complies with the conditions for pregnancy prevention *as* listed above, including confirmation that she has an adequate level of understanding.

The patient has acknowledged the aforementioned conditions.

Should pregnancy occur in spite of these precautions dunng treatment with Accutane or in the month following, there is a great risk of very severe malformation of the fetus (involving in particular the central nervous system, the heartland the large blood vessels). There is also an increased risk of spontaneous abortion, if pregnancy does occur, the physician and patient should discuss the advisability of continuing the pregnancy.

- **Contraception**

referred for contraceptive advice if they are not using effctive contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with Accutane, even in patients with amenorrh ea.

- **Pregnancytesting**

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/ ml are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

Prior to starting therapy:

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

A medically supervised pregnancy test should also be performed during the consultation when Accutane is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with Accutane.

Follow-up Visits:

· Follow-up visits should be arranged at 28 days intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patients sexual activity and recent menstrual history (abnormal menses, missed periods or amenorthea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit orin the 3 days prior tothevisatotheprescriber.

P End of treatment:

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

The pharmaolstmustensure that:

Prescriptions of Accutane for women of child-bearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Accutane should occur on the same day

should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Accutane should occur on the same day.

- Dispensing of Accutane should occur within a maximum of 7 days of the prescription.

Educational material

In order to assist prescribing physicians, pharmacists and patients in avoiding fetal exposure to Accutane, the manufacturer provides a Pregnancy prevention Programme (which needs to be locally approved) consisting of the following material to reinforce the warnings about the drug's teratogenicity and emphasizs the mandatory need for reliable contraception in female patients of child-bearinn potential,

For Physicians:

- Physician's Guide to Prescribing Accutane to Female patients
- PhysicianrsChecklistfor Prescribing to Female Patients
- Acknowledgement Form for Female Patients

For Patients:

- Patient information Brochure
- Contraception. The Facts you Need

For Pharmacists:

- Pharmacist's Guide to DispensingAccutane

Full Patient Information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Male Patients:

The availalbe data suggest that the level of maternal exposure from the semen and seminal fluid of the patients receiving Accutane is not of a sufficient magnitude to be associated with the teratogenic effects ofAccutane.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional Precautions

Microdosed progesterone preparations (minipills) may be an inadequate method of contraception during Accutane therapy. Patients should be instructed never to given this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Donation of blood by patients should be avoided during and within 1 month after cessation of Accutane treatment to prevent anaccidental exposure and the potential risk to the fetus of a pregnant transfusion receipient

Psychiatric disorders

Depression, psychotic symptoms and very rarely suicide attempts and suidde have been reported in patinets treated with Acoutane (see section 2.6 Undesirable Effects). A causal relationship has not been established for these events. Particular cam needs to be taken in patients with a history of depression and all patinets should be monitored for signs of deppression and referred for appropriate treatment if necessary. However, discontinuation of Accutane may not alleviate symptoms end 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 dose not require dose adjustment.

Exposure to intense sunlight ore UV rays hsould 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 treatmnet should be avoided in patients on Accutane and for a peced of 5-6 months after the end of treatment be-cause of the risk of hypertrophic scarring in atypical areas and more rarely hyper- or hypo-pigmentation in treated areas. Wax effilation should be avoided in patients on Accutane therapy and at east fora period of 6 months after treatmentdue to the possibility of epidermal stripping, scarring or dermatitis.

Concurrent administration of Accutane with topical keratolytic or exfolliative anti-acne agents should be avoided as local irritation may increase.

Patients should be advised to use a skin-moisturizing ointment or cream and a lip balm from the start of treatment as Accutane is likely to cause dryness of the skin and lips.

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

Eye disorders

Dry eyes, corneal opacities, decreased night vision, keratin, blepharitis and conjunctivitis usuallly resolve after discontinuation of therapy Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of Accutane considered. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment. Decreased night vision has occurred during Accutane therapy and in rare instances has persisted after discontinuation of therapy (see section 26 Undesirable Effects). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautions when driving or operating any vehicle at night. Visual problems should be carefully monitored.

Musculo-skeletal and connective tissue disorders

Myalgia, arthralgia and increased serum creature phosphokinase may occur and may be associated with reduced tolerance to vigorous exercise (see section 2.6 Undesirable Effects).

Bone changes, including premmature epiphyseal closure, hyperostosis and calcifications of tendons and ligaments have occurred after several years of administration at high doses for treating disorders of keratinization. The dose levels, duration of treatment and total cumulative dose in these patients generally far eticceded those recommended for the treatment of acne. Therefore, a careful evaluation of the risk/benefit ratio should be carried out in every patient.

Benign Intracranial hypertension

Rare cases of benign intracranial hypertension "pseudotumor cerebri" have been reported, some of which involved concomitant use of tetracyclines (see section 2.4.3 interactions with other medical products or other forms of intenaction). signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilledema. Patients who develop benign intracranial hypertension should discontinueAccutane immediately.

Therefor, concomitant treatment with tetracydince should be avoided.

Hepatobiliary disorders
Liver function or enzymes should be checked before and 1 month after the start of treatment, and subsequently at 3 months 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, when transaminase levels exceed the normal levels, reduction of the dose or discontinuation of treatment may be necessary.

Lipid metabofism
Serum lipids (fasting value) should also be checked, 1 month after the start of therapy, and subsequently et 3 months intervals unless more frequent monitoring is clinically indicated. The serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment. The changes in serum lipids may also resolve in response to control clinically significant serum triglycehde elevations, since levels in excess of 800 mg/dl or 9 mmol/lare sometimes associated with acute pancreatice, which is known to be potentially fatal (see section 26 Undesirable Effects). Hence, Accutane should be discontinued if uncontrolled hypertriglycendemia or symptoms of pancrcetitis occur.

Gastrointestinal disorders
Acculane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior
history of intestinal disorders. Patients experiencing severe (hemorrhagic)diarrhea should discontinue immediately.

Allergic reactions
Anaphylactic reactions have been rarely reported and only after previous topical exposure to retinoids. Allergic cutanous reactions are reported infrequently. Serious cases of allergic vasoursis. often with purpura (bruises and red patches) of the extremities and extracutanous involvement have been reported. Severe allergic reactions necessitate interruption of the rspy and careful monitoring.

High-risk patients
In highzisk patients with diabetes, obesity, alcoholism or lipid metabolism disorder undergoing treatment with Accutane, more frequent checks of serum values for lipids and/or blood glucose may be necessary
In known or suspected diabetics, frequent determination of blood glucose levels is recommended. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagonsed dudng Accutane therapy.

2.4.2 Ability to Drive and Use Machines
Decreased night vision has occurred during and after discontinuation of Accutane 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 any machine at night (see section 2.4 Warnings and Precautions).

2.4.3 Interactions with other medicinal products and other forms of Interaction
Concurrent therapy with Accutane and vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified.
Rare cases of benign intracranial hypertension "pseudotumor cerebri" have been reported, some of which involved concomitant use of tetracyclines. Therefore, concomitant treatment with tetracyclines should be avoided (see section 2.4 Wamings and Precautions).

2.5 Use in Special Populations

2.5.1 Pregnancy

Pregnancy is an absolute contraindication to treatment with Accutane. If Pregnancy does occur in spite of these precautions during treatment with Accutane or in the month following, there is a great risk of very severe and serious malformation of the fetus.

The fetal malformations associated with exposure to Accutane 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 (conotrunoal mafformations such as tetralogy of Pallet, 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 Accutane. treatment must be stopped and the patient should be referred tee physician specialized or experienced in teratology for evaluatio n and advice.

2.6.2 Nursing Mothers
As Accutane is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, the use of Accutane is contraindicated in nursing mothers.

2.5.3 Pediatric Use: The use of Accutane in pediatric patients less than 12 years of age has not been studied.

2.5.4 Renal Impairment
Severe renal insufficiency and renal failure do not effect the phermacokinetics of isotretinoin. Therefore Accutane 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 (see section 221 Special Dosage Instructions).

2.5.5 Hepatic Impairment: See section 24.1 Warnings and Precautions, General

2.6 Undesirable Effects
Some of the side effects associated with the us of Accutane are dose-related. With the recommended dosage, he risk benefit ratio is generally acceptable considering the seventy of the disease. The side effects are generally reversible after altering the dose or discontinuation of treatment, however, some may persist after treatment has stopped.
The adverse reactions listed below reflect the experience from investigational studies of Accutane, and the post-marketing experience. The relationship of some of these events to adverse reactions seen in patients receiving Accutane 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).

Symptoms associated with hypershaminosis A
The following symptoms are the most frequently reported undesirable effects with Accutane, dryness of the skin dryness of the mucosa e.g. of the lip, cheilitis, the nasal mucosa (epistaxis), the pharynx (hoarseness), the eyes (conjunctivits, reversible corneal opacities and intolerance to contact lenses).

Skin rod appendages disorders
Exanthema, pruritus, facial erythema/dermatitis, sweating, pyogenic granuloma, paronychia, nail dystrophy, increased formation of granulation tissue, persistent hair thinning, reversible alopecia, acne fulminans, hirsutism, hyperpigmentation, photosensitivity, photoallergic reactions, skin fragility Acne flare °occurs at the start of treatment and persists for several weeks.

Huscolo-skeletal system disordets
Myalgia (muscle pain) with or without elevated serum CPK values (see section 2.4 Warnings and Precautions), arthralgia (joint pain), hyperostceis, arthritis, calcification of ligaments and tendons and other bone changes, reduced bone density, back pain, epiphyses, premature fusion tendinitis.

Psychiatric and central moons system disorders
Behavioral disorders, depression (see section 2.4 Warnings and Precautions), suicide aftempt, suicide, headache, increased intracranial pressure (pseudotumor cerebn), seizures. Although a causal relationship has not been established, particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and relented for appropriate treatment if necessary.

Sensoty disorders
Isolated cases of visual disturbances, pholophobia, dark-adaptation disturbances (decreased night vision), rarely color vision disturbances (reversible upon discontinuation), lenticular cataract, keratitis, blurred vision, blepheritis, conjunctivitis, eye irritation, papilledema as sign of benign intracranial hypertension, impaired hearing at certain frequencies have been reported.

Gastro-inestinal system disorders
Nausea, severe diarrhea, inflammatory bowel disease such as colts, ileitis, and hemorrhage have been reported to occur. Patients treated with Accutane, especially those with high triglyceride levels, am at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (see section 2.4 wamings end Precautions).

Liver and bilialy system disorders
Transient and reversible increases in liver transaminases, some caces of hepattits. In many such cases the changes have been within the normal range and values have resumed to baseline levels during treatment. in other cases, however, it has been necessary to reduce the dose or d iscontinue treatment with Accutane.

Respiratiory system disorders
Bronchospasm has been rarely repoded; sometimes in patients with a pre-histroy of asthma.

Disorders of the blood
Decrease in white blood cell count, neutropenie, disorders of red blood cell parameters (such as decrease in red blood cell count and hematocrit, elevation of sedimentation rate), increase in platelet or decrease in platelet count (thrombocytopenia), anemia.

Laboratory findings
Increase in serum triglycedde and cholesterol levels, decrease in HDL, hyperuricemia. Rare cases of elevated blood glucose have been reported, and new cases of diabetes have been diagnosed (see section 2.4 Warnings and Precautions).

Resistance mechanism disorders (Infections)
Local or systemic infections due to gram-positive microorganisms (Staphylcceccus aureus).

3.2 Pharmacokinetic Properties
Since the kinetics of isotretinoin and its metabolites are linear, its plasma concentrations during therapy can be predicted from single dose data. This property also provides some evidence that the activity of hepatic drug metabolizing enzymes is not induced by isotretinoin.

3.2.1 Absorption
The absorption of isotretinoin from the gastro-intestinal tract is variable; the absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation kern dog studies would suggest a fairly low and variable systemic bioavailability. In acne patients at steady state, peak blood concentrations (Cmax) of 310 ng/ ml (range: 188-473 rig/ml) were observed 2-4 hours after dosing with 80 mg/day isotretinoin under fasting conditions. Plasma concentrations of isotretinoin are about 1.7 times those of blood concentrations due to poor penetration of isotretinoin into red blood cells.
When isotretinoin is taken with food, the bioavailabihty is doubled relative to fasting conditions.

3.2.2 Distribution
isotretinoin is extensively bound to plasma proteins, mainly albumin (>99.9%); therefore the free (= pharmacologically active) fraction of isotretinoin is less than 0.1% over a wide range of therapeutic concentrations.
The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use.
Steady-state blood concentrations (Cmin, ss) of isotrefinoin in patients with severe acne treated with 40mg b.i.d. ranged from 120-200 rig/ml; the concentration of 4-oxo-isotretinoin in these patients were 2-5 times higher than the isotretinoin concentrations. In humans lithe information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of these in serum.

3.2.3 Metabolism
After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isokelinoin, tretinoin (all-trans retinoic acid), and 4-oxo-isotretinoin. The major metabolite N 4-oxo isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound. Other mince metabolites have been detected but are not completely identified, which also includes glucuronide conjugates. Isotretinoin metabolites have shown biological activity in several in vitro-tests. Thus the observed clinical profile in patients could be the result of the pharmacological activity of isotretinoin and its metabolites.
Since isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolized (= interconverted), the metabolism of tretinoin is linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose N metablozied by isomerization.
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. Accutane and its metabolites do not significantly affect CYP activity.

3.2.4 Elimination
After oral administration of radiolabeled isotretinoin approximately equal fractions of the dose were recovered in urine and feces. 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 refinoid concentrations are reached within approximately lwo weeks following the end of Accutane therapy.

3.2.5 Pharmacoldnetics in Special Populations
Since Accutane is contraindicated in patients with hepatic impairment, limited information on the kinetics of Accutane is available in this patient population.

3.3 Preclinical Safety

3.3.1 Mutagenicity
Isotretinoin has not been shown to be mutagenic nor carcinogic in in vitro or in vivo animal tests, respectively.

3.3.2 Impairment of Fertility
Isotretinoin, N therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardize the formation and development of the embryo on the part of the men taking isotretinoin.

3.3.3 Tefatogenicity
Like other vitamin A derivatives, isotrctinoin has been shown in animal experiments to be teratogenic and embryotoxic.
Due to the teratogenic potential of isotretinoin them are therapeutic consequeces for the administration to women of a child-bearing age (see section 2.3 Contraindications, 2.4 Warnings and Precautions, and 2.5 Use in Special Populations).
3.3.4 Other

Acute toxicity
The acute oral toxicity of isotretinoin was determined in venous 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 23 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.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack.
Store in the original package in order to protect from moisture and light.

4.2 Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines
The release of pharmaceuticals in th environment should be minimized. Medicines should not be disposed of via waste water and disposal through household waste should be avoided. Use establised "collection systems" if available in your location.
return any unused Accutane capsules to the pharmacist.
Medicine: Keep out of reach and sight of children.

4.3 Pack Size
20mg Capsules
1x10's Blister Pack.
3x10's Blister Pack.

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں یا تفصیلی ہدایات کیلئے ڈبے کے اندر موجود پرچہ ملاحظہ کریں۔

ہدایات:
دوا کو کمرے کے درجہ حرارت پر رکھیں۔
دوا کو گرمی، نمی اور سورج کی روشنی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

انتباہ
حاملہ خواتین استعمال نہ کریں۔ دوران استعمال حاملہ ہونے سے گریز کریں۔
بتائی گئی ہدایت پر سختی سے عمل کریں۔

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