



PRODUCT MONOGRAPH

Accutane™ Roche®
(Isotretinoin)

10 mg and 40 mg capsules

Nodular/Inflammatory and Conglobate Acne Therapy

Hoffmann-La Roche Limited
2455 Meadowpine Boulevard
Mississauga, Ontario
L5N 6L7

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ACUTANE™ ROCHE®

(isotretinoin)

THERAPEUTIC CLASSIFICATION

Nodular/Inflammatory and Conglobate Acne Therapy

CAUTION: 'Accutane' (isotretinoin) is a known teratogen. When prescribing this drug to female patients of childbearing potential, physicians must use the manufacturer's Pregnancy Prevention Program™, which includes comprehensive information about the potential risks of this drug, a checklist for criteria which must be met prior to prescribing this drug to female patients of childbearing potential, detailed information on birth control options, a patient informed consent for review and signature, and monthly pregnancy reminders for physicians to use at each patient visit during the treatment period.

Some patients treated with 'Accutane' have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression during therapy. If symptoms of depression develop or worsen during treatment with 'Accutane', the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary.

Information concerning the Pregnancy Prevention Program™ has also been provided directly to patients via the 'Accutane' compliance packaging. This "Patient Information" asks female patients of childbearing potential, who have not been counselled using the Pregnancy Prevention Program™, to contact their physician for further information.

Patients should also be informed that confidential contraception counselling (provided by a health care professional) is available from the manufacturer.

ACTION AND CLINICAL PHARMACOLOGY

The mechanism of action of 'Accutane' (isotretinoin) is unknown. Vitamin A is important for functional integrity of the skin and is known to affect the keratinization process. In acne patients, improvement occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to either the dose or duration of 'Accutane' administration and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

Following oral administration of 80 mg, peak plasma concentrations ranged from 167 to 459 ng/mL (mean 256 ng/mL) with a mean time to peak of 3.2 hours in volunteers, while in acne patients peak plasma concentrations ranged from 98 to 535 ng/mL (mean 262 ng/mL) with a mean time to peak of 2.9 hours. Isotretinoin is 99.9% protein bound in human plasma, almost exclusively to albumin. The mean terminal elimination half-life of isotretinoin in patients with acne has a mean value of 19 hours. Following oral administration of ¹⁴C-isotretinoin, ¹⁴C activity in blood declined with a mean half-life of 90 hours. Approximately equal amounts of radioactivity were recovered in the urine and feces, with 65-83% of the dose recovered.

When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions (see DOSAGE AND ADMINISTRATION).

The major metabolite identified in blood and urine was 4-oxo-isotretinoin. Tretinoin and 4-oxo-tretinoin were also observed. The apparent half-life for elimination of the 4-oxo-isotretinoin ranged from 11 to 50 hours, with a mean of 28 hours. Following 80 mg of isotretinoin administered orally, maximum plasma concentrations of the 4-oxo-isotretinoin was 87 to 399 ng/mL and maxima were observed between 6 and 20 hours. The blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours. The data suggest that both isotretinoin and the major metabolite are excreted in the bile and reabsorbed.

The mean minimum steady-state blood concentrations of isotretinoin were 160 ng/mL in 10 patients receiving 40 mg b.i.d. doses. After single and multiple doses, the mean ratio of areas under the curves of 4-oxo-isotretinoin to isotretinoin was between 3 and 3.5.

INDICATIONS

'Accutane' (isotretinoin) is indicated for the treatment of:

- Severe Nodular and/or Inflammatory Acne
- Acne Conglobata
- Recalcitrant Acne

Because of significant side effects associated with its use, 'Accutane' should be reserved for patients where the conditions listed above are unresponsive to conventional first line therapies. 'Accutane' should only be prescribed by physicians knowledgeable in the use of retinoids systemically, who understand the risk of teratogenicity in females of child bearing age and who are experienced in counseling young adults for whom 'Accutane' is generally indicated. A careful assessment of the patient's mental state should be made, including whether or not they have a history of previous psychiatric illness (see CONTRAINDICATIONS, PRECAUTIONS, WARNINGS). It is strongly recommended that each 'Accutane' prescription be limited to a one-month supply in order to encourage patients to return for follow-up to monitor side-effects.

CONTRAINDICATIONS

'Accutane' (isotretinoin) is contraindicated in pregnancy. Females must not become pregnant while taking 'Accutane' or for at least one month after its discontinuation. 'Accutane' causes severe birth defects in a very high percentage of infants born to women who take this drug even for a short period of time during pregnancy (see WARNINGS - Pregnancy, Pregnancy Testing, Contraception).

'Accutane' is contraindicated in females of childbearing potential unless all of the following conditions apply:

1. The patient has severe disfiguring nodular and/or inflammatory acne, acne conglobata or recalcitrant acne that has not responded to standard therapy, including systemic antibiotics.
2. The patient is reliable in understanding and carrying out instructions.

3. The patient is able and willing to comply with the mandatory effective contraceptive measures.
4. The patient has received, and acknowledged understanding of, a careful oral and printed explanation of the hazards of fetal exposure to 'Accutane' and the risk of possible contraception failure. This explanation may include showing a line drawing to the patient of an infant with the characteristic external deformities resulting from 'Accutane' exposure during pregnancy.
5. The patient uses effective contraception without any interruption for one month before beginning 'Accutane' therapy, during 'Accutane' therapy and for one month following discontinuation of 'Accutane' therapy. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method (see WARNINGS - Pregnancy, Pregnancy Testing and Contraception and PRECAUTIONS - Contraceptives).
6. The patient has had two negative pregnancy tests before starting 'Accutane' therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for 'Accutane' therapy by the physician. The patient has had a second serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL with a negative result, performed in a licensed laboratory, within 11 days prior to initiating therapy. The patient has had two or three days of the next normal menstrual period before 'Accutane' therapy is initiated.
7. In the event of relapse treatment, the patient must also use the same uninterrupted and effective contraceptive measures one month prior to, during and for one month after 'Accutane'.

(Re items 2 to 7 see WARNINGS - Pregnancy, Pregnancy Testing, Contraception).

Even female patients who normally do not employ contraception due to a history of infertility should be advised to do so while taking 'Accutane', following the above guidelines.

'Accutane' is also contraindicated in hepatic and renal insufficiency, hypervitaminosis A, and in patients with excessively elevated blood lipid values.

'Accutane' is also contraindicated in patients who are sensitive to parabens or to those with known hypersensitivity to retinoids or any component of the 'Accutane' capsules.

WARNINGS

Pregnancy, Pregnancy Testing and Contraception: There is an extremely high risk (25% or greater) that major human fetal abnormalities will occur if pregnancy occurs during treatment with 'Accutane' (isotretinoin) or up to one month following its discontinuation. Potentially any exposed fetus can be affected. These abnormalities, associated with 'Accutane' administration during pregnancy, have been reported and include:

CNS (hydrocephalus, hydranecephaly, microcephaly, posterior fossa abnormalities, cranial nerve dysfunction, cerebellar malformation); craniofacial (anotia, microtia, low set ears, small or absent external auditory canals, microphthalmia, facial dysmorphism, cleft palate); cardiac (septal defects, aortic arch abnormalities, tetralogy of Fallot); thymus gland abnormalities; and parathyroid hormone deficiency.

Female patients of childbearing potential must not be given 'Accutane' until pregnancy is excluded. The patient must have two negative pregnancy tests before starting 'Accutane' therapy with the first pregnancy test conducted at initial assessment when the patient is qualified for 'Accutane' therapy by the physician. A second pregnancy test must be performed within 11 days prior to starting 'Accutane' treatment. 'Accutane' treatment should start on the second or third day of the next normal menstrual period following this negative pregnancy test. Effective contraception must be used for at least one month before starting 'Accutane' treatment, during treatment and for at least one month following the discontinuation of 'Accutane' treatment. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method (see PRECAUTIONS - Contraceptives). Pregnancy occurring during treatment with 'Accutane' and for one month after its discontinuation, carries the risk of fetal malformation and the increased risk of spontaneous abortion (see WARNINGS above and TOXICOLOGY - Reproduction and Teratology Studies). Females should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment. If pregnancy does occur during this time the physician and patient should discuss the desirability of continuing the pregnancy.

It is strongly recommended that all female patients of childbearing potential treated with 'Accutane' have regular monthly pregnancy tests during treatment and one month after the discontinuation of treatment. These pregnancy tests will:

- a) Serve primarily to reinforce to the patient the necessity of avoiding pregnancy.
- b) In the event of accidental pregnancy, provide the physician and patient an immediate opportunity to discuss the serious risk to the fetus from this exposure to 'Accutane' and the desirability of continuing the pregnancy in view of the potential teratogenic effect of 'Accutane' (see WARNINGS above and TOXICOLOGY - Reproduction and Teratology Studies).

Nursing Mothers: It is not known whether isotretinoin is excreted in human milk. As isotretinoin is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, women should not breast-feed if they are receiving 'Accutane'.

Psychiatric Disorders: Depression, psychotic symptoms and, rarely, suicide attempts, suicide, and aggressive and/or violent behaviours have been reported in patients treated with 'Accutane'. Although a causal relationship has not been established, particular care should be taken in patients with a history of depression. All patients should be screened and monitored for signs of depression. If symptoms of depression develop or worsen during treatment with 'Accutane', the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment.

Hyperostosis: Due to possible occurrence of bone changes, a careful evaluation of the risk/benefit ratio should be carried out in every patient and 'Accutane' administration should be restricted to severe cases of acne. In clinical trials of disorders of keratinization, with a mean dose of 2.24 mg/kg/day, a high prevalence of skeletal hyperostosis was noted. Two children showed x-ray findings suggestive of premature closure of the epiphysis. Additionally, skeletal hyperostosis was noted in six of eight patients in a prospective study of disorders of keratinization. Minimal skeletal hyperostosis has also been observed by x-rays in prospective studies of cystic acne patients treated with a single course of therapy at recommended doses.

Hepatotoxicity: Liver function tests should be monitored before treatment and at regular

intervals during treatment (one month after the start of treatment and at least three month intervals thereafter). Several cases of clinical hepatitis have been noted which are considered to be possibly or probably related to 'Accutane' therapy. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, 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 'Accutane', the drug should be discontinued and the etiology further investigated.

Acute Pancreatitis: There have been some reports of acute pancreatitis, which is known to be potentially fatal. This is sometimes associated with elevation of serum triglycerides in excess of 800 mg/dL (see ADVERSE REACTIONS). Therefore, every attempt should be made to control significant triglyceride elevation (see PRECAUTIONS - Lipids). 'Accutane' should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

PRECAUTIONS

General: Before starting therapy with 'Accutane' (isotretinoin), physicians should determine whether the patient may be depressed or has a history of depression, including a family history of major depression.

Benign Intracranial Hypertension (Pseudotumor cerebri): 'Accutane' has been associated with a number of cases of benign intracranial hypertension, some of which involved concomitant use of tetracyclines (see PRECAUTIONS - Drug Interactions and ADVERSE REACTIONS - Clinical Adverse Experiences). Early signs and symptoms of this disorder usually include headache, visual disturbances, nausea and vomiting. Patients with these symptoms should be examined for papilledema. If present, 'Accutane' should be discontinued immediately and the patient referred to a neurologist for diagnosis and care.

Decreased Night Vision: A number of cases of decreased night vision have occurred during 'Accutane' therapy and in rare instances have persisted after therapy (see ADVERSE REACTIONS - Clinical Adverse Experiences). 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. Visual problems should be carefully monitored.

Hearing Impairment: Impaired hearing at certain frequencies has been reported in some patients treated with 'Accutane'.

Eye Disorders: Corneal opacities have occurred in patients receiving 'Accutane' for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. Dry eyes, corneal opacities, and keratitis usually resolve after discontinuation of therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. All 'Accutane' patients experiencing visual difficulties should discontinue the drug and have an ophthalmological examination. (see ADVERSE REACTIONS).

Inflammatory Bowel Disease: 'Accutane' has been temporally associated with inflammatory bowel disease (including regional ileitis, colitis and hemorrhage) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue 'Accutane' immediately.

Special Patient Groups: In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with 'Accutane', more frequent checks of serum values for lipids (see WARNINGS - Pancreatitis) and/or blood glucose may be necessary.

Lipids: Serum blood lipid determinations (under fasting conditions) should be performed before 'Accutane' is given and then at intervals (one month after the start of therapy) until the lipid response to 'Accutane' is established (which usually occurs within four weeks), and also at the end of treatment.

Approximately 25% of patients receiving 'Accutane' experienced an elevation in plasma triglycerides. Approximately 15% developed a decrease in high density lipoproteins and about 7% showed an increase in cholesterol levels. These effects on triglycerides, HDL and cholesterol were reversible upon reduction of the dose or cessation of 'Accutane' therapy (see ADVERSE REACTIONS-Laboratory Abnormalities).

Patients with increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake and familial history.

The cardiovascular consequences of hypertriglyceridemia are not well understood, but may increase the patient's risk status. Therefore, every attempt should be made to control significant triglyceride elevation. 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 'Accutane'. An obese male patient with Darier's disease developed elevated triglycerides and subsequent eruptive xanthomas.

Diabetes: Patients with diabetes or a family history of diabetes may experience problems with the control of their blood sugar during 'Accutane' therapy. Therefore, known or suspected diabetics should have periodic blood sugar determinations. Although no causal relationship has been established, elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during 'Accutane' therapy (see ADVERSE REACTIONS - Laboratory Abnormalities).

Drug Interactions:

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

Tetracyclines: Rare cases of benign intracranial hypertension 'pseudotumor cerebri' have been reported after use of 'Accutane' and/or tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see PRECAUTIONS - Benign Intracranial Hypertension and ADVERSE REACTIONS - Clinical Adverse Experiences).

Children: The long-term safety of 'Accutane' in prepubertal children has not been established.

Blood Donation: It is recommended that blood donation for transfusion purposes be deferred during therapy with 'Accutane' and for one month after discontinuation of treatment. Theoretically, blood from such donors could present a small risk to the fetus if transfused to a pregnant mother during the first trimester of pregnancy.

Contraceptives: Microdosed progesterone preparations (minipills) are not a suitable method of contraception during 'Accutane' therapy.

Aggressive Dermabrasion: It is recommended that aggressive dermabrasion be avoided in patients on 'Accutane' and for a period of 5-6 months after treatment because of the risk of hypertrophic scarring in atypical areas.

Wax Epilation: It is recommended that wax epilation be avoided in patients on 'Accutane' and for a period of 5-6 months after treatment because of the risk of scarring or dermatitis.

Myalgia / Arthralgia: Myalgia and arthralgia (mild to moderate) may occur and may be associated with reduced tolerance to vigorous exercise (see ADVERSE REACTIONS). Instances of raised serum creatine phosphokinase (CPK) values have been reported in patients receiving 'Accutane', particularly those undertaking vigorous physical activity. Discontinuation of 'Accutane' may be required.

Anaphylactic Reactions: Anaphylactic reactions have been reported. These reactions were more serious after prior exposure to topical retinoids. Allergic cutaneous reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

ADVERSE REACTIONS

Many of the side effects and adverse reactions seen or expected in patients receiving 'Accutane' are similar to those described in patients taking high doses of vitamin A.

Dose-Relationship and Duration:

Cheilitis and hypertriglyceridemia are usually dose related.

Adverse reactions were generally reversible when therapy was discontinued; however, some have persisted after cessation of therapy.

Clinical Adverse Experiences:

The most common side-effects are mucocutaneous or dermatologic. The common side effects include: cheilitis (96%), facial erythema/dermatitis (55%), dry nose (51%), desquamation (50%), pruritus (30%), dry skin (22%), conjunctivitis (19%), alopecia (13%), irritation of the eyes (11%), rash (<10%). Dryness of the nasal mucosa and pharynx may be associated with mild epistaxis and hoarseness, respectively. Mild-to-moderate conjunctivitis may be alleviated by use of an ophthalmic ointment. In rare cases, hair loss persisted after treatment was completed.

Approximately 13% of patients experience joint pain during treatment.

Peeling of palms and soles, skin infections, increased susceptibility to sunburn, nonspecific urogenital symptoms, nonspecific gastrointestinal symptoms, headache, fatigue occur in approximately 5% of patients.

Skeletal hyperostosis has been observed on x-rays of patients treated with 'Accutane' (see WARNINGS - Hyperostosis).

'Accutane' has been associated with a number of cases of pseudotumor cerebri, some of which involved concomitant use of tetracyclines (see PRECAUTIONS - Benign Intracranial Hypertension and Drug Interactions).

Of 72 patients who had normal pretreatment ophthalmological examinations, five developed corneal opacities while on 'Accutane' (all five patients had a disorder of keratinization). Corneal opacities have also been reported in nodular and/or inflammatory acne patients treated with 'Accutane' (see PRECAUTIONS - Eye Disorders). Decrease in night vision has been reported and in rare instances has persisted (see PRECAUTIONS - Decreased Night Vision). Cataracts and visual disturbances have also been reported.

'Accutane' has been temporally associated with inflammatory bowel disease, including regional ileitis, colitis and hemorrhage (see PRECAUTIONS - Inflammatory Bowel Disease).

Other adverse reactions which have been reported include:

Mucocutaneous and Dermatologic: flushing, changes in skin pigment, urticaria, bruising, disseminated herpes simplex, hair problems (other than thinning), hirsutism, erythema nodosum, paronychia, nail dystrophy, pyogenic granuloma, bleeding and inflammation of the gums, acne fulminans, exanthema, sweating, increased formation of granulation tissue, photoallergic/photosensitizing reactions, skin fragility. Acne flare occurs at the start of treatment and persists for several weeks.

CNS: seizures, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy, paresthesia.

Psychiatric Disorders: Depression, psychotic symptoms and, rarely, suicide attempts, suicide, and aggressive and/or violent behaviours (see WARNINGS - Psychiatric Disorders). Depression has been reported during and after therapy. In some of these patients, depression has subsided with discontinuation of therapy and recurred when 'Accutane' therapy was reintroduced. Emotional instability has been reported with 'Accutane'.

Ophthalmologic: optic neuritis, photophobia, eye lid inflammation, keratitis, and colour vision disturbances. Dry eyes and/or decreased tolerance to contact lenses have also been reported during therapy. In some instances these conditions have persisted after cessation of therapy.

Gastrointestinal: nausea, mild gastrointestinal bleeding, rectal bleeding.

Patients treated with 'Accutane' especially those with high triglyceride levels are at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (see WARNINGS - Acute Pancreatitis).

Cardiovascular: edema, transient pain in the chest, palpitations, tachycardia.

Respiratory: respiratory infections.

Bronchospasm has been rarely reported; sometimes in patients with pre-history of asthma.

Reproductive system: abnormal menses.

Urinary system: glomerulonephritis

Hematological: hematuria/proteinuria

Body as a whole: weight loss, anemia, lymphadenopathy, vasculitis including Wegener's granulomatosis, allergic vasculitis, allergic responses, and systemic hypersensitivity.

Musculoskeletal: arthritis, muscle pain (myalgia; elevations of serum CPK values), arthralgia, calcification of ligaments and tendon and tendinitis.

Hearing: impaired hearing at certain frequencies.

Laboratory Abnormalities:

'Accutane' therapy induces changes in serum lipids in a significant number of treated subjects. These changes consisted of: elevation of serum triglycerides (25% of patients), mild to moderate decrease in serum high density lipoprotein (HDL) (16% of patients), and minimal elevations of serum cholesterol (7% of patients). Abnormalities of serum triglycerides, HDL and cholesterol were reversible upon cessation of 'Accutane' therapy.

Cases of elevated blood glucose have been reported, and new cases of diabetes have been diagnosed (see PRECAUTIONS - Diabetes).

A rise in serum levels of liver enzymes may occur, especially with higher dosages. Although the changes have usually been within the normal range, and may return to baseline levels despite continued treatment, significant increases have occurred in a few cases, necessitating dosage reduction or discontinuation of 'Accutane' (see WARNINGS - Hepatotoxicity). An elevated erythrocyte sedimentation rate may also occur (40% of patients).

Other less commonly reported laboratory abnormalities were: Elevated fasting blood sugar, elevated CPK, and hyperuricemia. Decreases in red blood cell parameters, decreases in white blood cell counts, elevated sedimentation rates and elevated platelet counts. White blood cells in the urine, proteinuria, and red blood cells in the urine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of acute 'Accutane' (isotretinoin) overdose evacuation of the stomach should be considered during the first few hours after this overdose. Signs and symptoms of acute overdose have been associated with headache, vomiting, facial flushing, cheilitis, abdominal pain, dizziness and ataxia. To date, all symptoms have quickly resolved without apparent residual effects and usually without treatment. Elevated intracranial pressure has been reported with patients receiving therapeutic doses of 'Accutane'. Patients with an 'Accutane' overdose should be monitored closely for signs of increased intracranial pressure. Signs of hypervitaminosis A could appear in cases of overdose.

Limited data exists on the pharmacokinetic characteristics of isotretinoin in an overdose situation. Following the oral administration of single 80, 160, 240 and 340 mg doses to 12

healthy male subjects C_{max} was 366, 820, 1,056 and 981 ng/mL, and $t_{1/2}$ was 13.6, 14.1, 14.4 and 16.5 hours for isotretinoin, respectively (Colburn et al 1985). Twenty-three compromised cancer patients received weekly oral doses of 200 (3 patients); 400 (7 patients); 660 (2 patients); 1,000 (3 patients); 1,400 (6 patients) and 1,800 (1 patient) mg/m². Normal body surface area for healthy subjects is 1.73 m². After the first dose, C_{max} was 1.5, 3.8, 3.5, 2.5, 2.7 and 4.6 µg/mL, and $t_{1/2}$ was 45, 9.1, 14.5, 57, 13.1 and 6.1 hours for isotretinoin, respectively (Clamon et al 1985). The absorption of isotretinoin appears to be a saturable process.

Since it is difficult to extrapolate from the results of these studies to the overdose situation, the following precautions should be taken with all female patients of childbearing potential who have taken an overdose of 'Accutane'.

1. At the time of the overdose, a pregnancy test must be performed and a blood sample collected for the determination of isotretinoin and metabolite concentrations.
2. One complete menstrual cycle after the overdose, a second pregnancy test must be performed and a second blood sample collected for the determination of isotretinoin and metabolite concentrations.
3. Effective contraception must be used for at least one complete menstrual cycle after the overdose and continued longer, if necessary until isotretinoin and its metabolites are no longer measurable in the blood.

Patients who present with a positive pregnancy test at the time of the overdose, one complete menstrual cycle after the overdose, or while isotretinoin or metabolite blood concentrations are measurable, should be fully counselled on the serious risk to the fetus from this exposure to 'Accutane' and the physician and patient should discuss the desirability of continuing the pregnancy. (See CONTRAINDICATIONS, WARNINGS, TOXICOLOGY - Reproduction and Teratology Studies).

Canadian Regional Poison Information Centres have been advised on the proper collection and handling of 'Accutane' blood samples and also on the laboratory(s) equipped to assay these samples.

DOSAGE AND ADMINISTRATION

The therapeutic response to 'Accutane' (isotretinoin) is dose-related and varies between patients. This necessitates individual adjustment of dosage according to the response of the condition and the patient's tolerance of the drug. In most cases, complete or near-complete suppression of acne is achieved with a single 12 to 16 week course of therapy. If a second course of therapy is needed, it can be initiated eight or more weeks after completion of the first course, since experience has shown that patients may continue to improve while off the drug.

Initial Therapy:

The initial dose of 'Accutane' should be individualized according to the patient's weight and severity of the disease.

In general, patients initially should receive 'Accutane' 0.5 mg/kg body weight daily for a period of two to four weeks, when their responsiveness to the drug will usually be apparent. It should be noted that transient exacerbation of acne is occasionally seen during this initial period.

The daily dosage should be taken with food in the nearest number of whole capsules, either as a single dose or in two divided doses during the day, whichever is more convenient.

Maintenance Therapy:

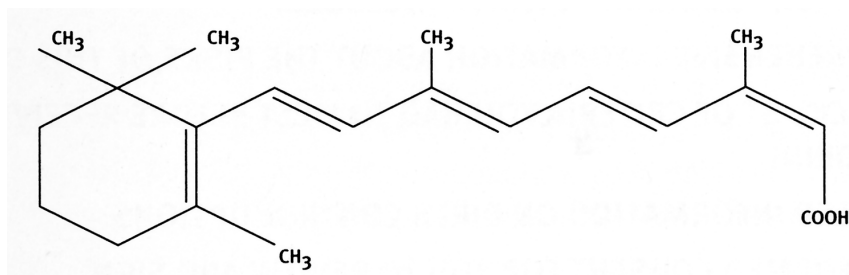
Maintenance dose should be adjusted between 0.1 and 1 mg/kg body weight daily and, in exceptional instances, up to 2 mg/kg body weight daily, depending upon individual patient response and tolerance to the drug.

A complete course of therapy consists of 12-16 weeks of 'Accutane' administration.

Patients may show additional improvement for up to several months after a course of 'Accutane' has been completed. With effective treatment, appearance of new lesions will not normally be evident for a period of at least three to six months.

PHARMACEUTICAL INFORMATION**Drug Substance:**

Structural Formula:



Proper Name:	Isotretinoin
Molecular Formula:	C ₂₀ H ₂₈ O ₂
Molecular weight:	300.44
Chemical Name:	3-7-dimethyl-9-(2,6,6-trimethyl-1-cyclo-hexen-1-yl)-2,4,6,8-nonatetraenoic acid.
Description:	Orange crystalline powder, insoluble in water; soluble in chloroform (10g / 100 mL). Melting point approximately 175°C; pKa approximately 4.

Dosage Forms:

'Accutane' 'Roche' 10: Reddish-violet opaque, oval-shaped soft gelatin capsules containing 10 mg isotretinoin, imprinted 'ROA 10'.

Non-medicinal ingredients (alphabetical order): beeswax, canthaxanthin, gelatin, glycerin, hydrogenated hydrolysed starch, mannitol, soybean and hydrogenated soybean oil, sorbitol, titanium dioxide.

'Accutane' 'Roche' 40: Yellow opaque, oval-shaped soft gelatin capsules containing 40 mg isotretinoin, imprinted 'ROA 40'.

Non-medicinal ingredients (alphabetical order): beeswax, gelatin, glycerin, methylparaben, propylparaben, quinoline yellow WS, soybean and hydrogenated soybean oil, sunset yellow FCF, titanium dioxide.

Package Sizes & Storage:

'Accutane' 'Roche' capsules 10 mg and 40 mg are available in blister packages of 30 capsules. They should be stored at 15-30°C and protected from light.

INFORMATION FOR THE CONSUMER

Accutane™ Roche® (isotretinoin) Capsules

Read this Information for the Consumer every time you get a prescription or a refill for 'Accutane'. There may be new information. This information does not take the place of talking with your doctor.

What is the most important information you should know about 'Accutane'?

'Accutane' is a medicine used to treat severe acne (nodular and or inflammatory acne) that cannot be cleared up by other acne treatments, including antibiotics. However, 'Accutane' can cause serious side effects. Before starting 'Accutane', discuss with your doctor how bad your acne is, the possible benefits of 'Accutane', and its possible side effects, to decide if 'Accutane' is right for you. Your doctor will ask you to read and sign a form indicating you understand some of the serious risks of 'Accutane'.

Possible serious side effects of taking 'Accutane' include *birth defects* and *mental health problems*.

All Females: Birth defects:

'Accutane' can cause birth defects (deformed babies) if taken by a pregnant woman. It can also cause miscarriage, premature birth, or death of the baby. Do not take 'Accutane' if you are pregnant or plan to become pregnant while being treated, and for at least 1 month after therapy. Also, if you get pregnant while taking 'Accutane', stop taking it right away and call your doctor.

All females should read the section in this Information for the Consumer:

"What are the important warnings for females taking 'Accutane'?"

All Patients: Mental health problems and suicide:

Some patients, while taking 'Accutane' or soon after stopping 'Accutane', have become depressed or developed other serious mental health problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking 'Accutane' have had thoughts about putting an end to their own lives (suicidal thoughts), tried to end their own lives, and some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on 'Accutane' becoming aggressive or violent. No one knows if 'Accutane' caused these behaviors or if they would have happened even if the person did not take 'Accutane'.

All patients should read the section in this Information for the Consumer:

"What special symptoms you must immediately tell your doctor about – Signs of mental health problems:"

For other possible serious side effects of 'Accutane', see:

"What special symptoms you must immediately tell your doctor about:"

What are the important warnings for females taking 'Accutane'?

'Accutane' CAN CAUSE DEFORMED BABIES. THERE IS AN EXTREMELY HIGH RISK THAT YOUR BABY WILL BE DEFORMED IF YOU ARE PREGNANT WHILE TAKING 'Accutane'. THIS RISK EXISTS EVEN IF 'Accutane' IS TAKEN FOR A SHORT TIME. IF YOU ARE A FEMALE OF CHILDBEARING POTENTIAL, YOUR PHYSICIAN SHOULD HAVE DISCUSSED THIS RISK WITH YOU, AND EXPLAINED HOW TO AVOID BECOMING PREGNANT WHILE TAKING 'Accutane'.

- **DO NOT TAKE 'Accutane' IF YOU ARE OR MAY BECOME PREGNANT DURING YOUR 'Accutane' TREATMENT.**
- **YOU MUST AVOID BECOMING PREGNANT WHILE YOU ARE TAKING 'Accutane' AND FOR AT LEAST ONE MONTH AFTER YOU STOP TAKING 'Accutane'.**
- **YOU MUST DISCUSS EFFECTIVE BIRTH CONTROL WITH YOUR DOCTOR BEFORE BEGINNING 'Accutane' TREATMENT, AND YOU MUST USE EFFECTIVE BIRTH CONTROL:**
 - **FOR AT LEAST ONE MONTH BEFORE YOU START 'Accutane';**
 - **WHILE YOU ARE TAKING 'Accutane'; AND**
 - **FOR AT LEAST ONE MONTH AFTER YOU STOP TAKING 'Accutane';****BEARING IN MIND THAT ANY METHOD OF BIRTH CONTROL CAN FAIL.**
- **IT IS RECOMMENDED THAT YOU EITHER ABSTAIN FROM SEXUAL INTERCOURSE OR USE TWO RELIABLE METHODS OF BIRTH CONTROL AT THE SAME TIME.**
- **DO NOT TAKE 'Accutane' UNTIL YOU ARE SURE THAT YOU ARE NOT PREGNANT.**
- **YOU MUST HAVE TWO NEGATIVE PREGNANCY TESTS BEFORE YOU START 'Accutane', BE ASSESSED ON A MONTHLY BASIS WHILE ON THE DRUG AND ONE MONTH AFTER THE TERMINATION OF 'Accutane'. IF YOUR MENSTRUAL PERIOD IS ABNORMAL IN LENGTH AND INTENSITY, FIRST CONTACT YOUR DOCTOR. (See the 'Accutane' PREGNANCY PREVENTION PLAN)**
- **YOU MUST WAIT UNTIL THE SECOND OR THIRD DAY OF YOUR NEXT NORMAL MENSTRUAL PERIOD BEFORE YOU START 'Accutane'.**

- **STOP TAKING 'Accutane' AND CONTACT YOUR DOCTOR IMMEDIATELY IF YOU DO BECOME PREGNANT WHILE TAKING 'Accutane' OR DURING THE FIRST MONTH AFTER TREATMENT HAS STOPPED, IF YOU MISS YOUR PERIOD, OR IF YOU HAVE SEXUAL INTERCOURSE WITHOUT USING EFFECTIVE BIRTH CONTROL. YOU SHOULD DISCUSS WITH YOUR DOCTOR THE SERIOUS RISK OF YOUR BABY HAVING SEVERE BIRTH DEFORMITIES BECAUSE YOU ARE TAKING OR HAVE TAKEN 'Accutane'. YOU SHOULD ALSO DISCUSS THE DESIRABILITY OF CONTINUING WITH YOUR PREGNANCY.**
- **DO NOT BREAST FEED WHILE TAKING 'Accutane'.**

You should have been counseled using the manufacturer's Pregnancy Prevention Program[®] which includes:

- Comprehensive information about the risks of this drug
- A line drawing of a deformed baby
- A checklist of criteria you had to meet before receiving this drug
- Detailed information on birth control options
- A chart: "Accutane Pregnancy Prevention Plan"
- An informed consent for you to review and sign

Please note that the manufacturer of 'Accutane' provides confidential contraception counseling (from a health care professional). For more information, please contact Hoffmann-La Roche Limited.

If you were not counseled using the "Pregnancy Prevention Program[®]", please contact your doctor for more information.

All patients should read the rest of this Information for the Consumer.

Do not take 'Accutane' unless you completely understand its possible risks and are willing to follow all of the instructions in this Information for the Consumer.

What should you tell your doctor before starting 'Accutane'?

- Tell your doctor if, you or someone in your family has ever had any mental illness, including depression, suicidal behavior, or psychosis. Psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there. Also, you should tell your doctor if you are taking medicines for any of these problems.
- Tell your doctor if you or any member of your family have liver disease, kidney disease, heart disease or high cholesterol or, diabetes or asthma.
- Tell your doctor if you plan vigorous physical activity during treatment with 'Accutane'.
- Tell your doctor if you are sensitive to parabens or any of the other nonmedicinal ingredients in Accutane listed at the end of this document or if you have any food or drug allergies.
- Tell your doctor if you are taking any vitamin preparations or health food supplements that contain Vitamin A.
- Tell your doctor the brand of contraceptives you are taking. There are certain types of contraceptives that should not be taken while on 'Accutane'.
- Tell your doctor if you are taking an antibiotic (particularly tetracyclines).

What should you avoid while taking 'Accutane'?

Females:

- **Do not get pregnant** while taking 'Accutane'. See "What is the most important information you should know about 'Accutane'?" and "What are the important warnings for females taking 'Accutane'?"
- **Do not breast feed** while taking 'Accutane' and for 1 month after stopping 'Accutane'. We do not know if 'Accutane' can pass through your milk and harm the baby.
- **Do not use low dose birth control pills.** They may not work while you take 'Accutane'.

All Patients:

- **Do not give blood** while you take 'Accutane' and for 1 month after stopping 'Accutane'. If someone who is pregnant gets your donated blood, her baby may be exposed to 'Accutane' and may be born with birth defects.
- **Do not take Vitamin A** supplements. Vitamin A in high doses has many of the same side effects as 'Accutane'. Taking both together may increase your chance of getting side effects.
- **Do not have cosmetic procedures to smooth your skin, such as waxing, dermabrasion, or laser procedures, while you are using 'Accutane' and for at least 6 months after you stop.** 'Accutane' can increase your chance of scarring or inflammation of the skin from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.
- **Avoid the use of artificial ultraviolet lights** such as the ones used in tanning machines and **protect yourself from excessive sunlight.** 'Accutane' may make your skin more sensitive to ultraviolet light.
- **Do not share 'Accutane' with other people.** It can cause birth defects and other serious health problems.
- **Do not take antibiotics with 'Accutane' unless you talk to your doctor.** For some antibiotics, you may have to stop taking 'Accutane' until the antibiotic treatment is finished. Use of both drugs together can increase the chances of getting increased pressure in the brain. Certain antibiotics interfere with the effectiveness of birth control pills

What special symptoms you must immediately tell your doctor about:

Serious side effects have been reported with 'Accutane'. It is important to watch for the symptoms listed below as they may be signs of serious side effects. **If you get these symptoms, you must tell your doctor immediately because it may be necessary to stop 'Accutane'.** These symptoms could lead to serious health problems requiring treatment even if 'Accutane' is stopped

Signs of mental health problems:

- changes in your mood such as becoming depressed, feeling sad, or having crying spells,
- losing interest in your usual activities,
- changes in your normal sleep patterns,

- becoming more irritable or aggressive than usual (for example, temper outbursts, thoughts of violence).
- losing your appetite,
- becoming unusually tired,
- having trouble concentrating,
- withdrawing from family and friends,
- having thoughts about taking your own life (suicidal thoughts).

Your doctor may recommend a consultation with a specialist if you become depressed or experience these changes in mood.

- **Signs of hypertension in your head:** bad headaches, blurred vision, dizziness, nausea, vomiting.
- **Signs of inflammation of the liver, pancreas, or intestines (bowel):** severe stomach pain, diarrhea, rectal bleeding; yellowing of the skin or eyes and/or dark urine.
- Changes in your **hearing** or ringing in your ears.
- Changes in your **vision** especially at night
- Persistent feelings of **dry eyes**
- **Signs of bone changes:** aches or pains in bones or joints, or difficulty in moving. If a bone breaks tell your doctor.
- **Signs of allergy to 'Accutane':** hives, swollen face or mouth, trouble breathing, fever, rash, red patches, bruises.
- **Signs of changes in your blood sugar levels:** fainting, become very thirsty, urinating a lot, feeling weak.
- Leg swelling, seizures (convulsions), slurred speech, problems moving or any other serious unusual problems.

'Accutane' may affect blood fat, cholesterol, or sugar levels. Therefore it is important for you to see your doctor at regularly scheduled visits.

What are the other possible side effects of 'Accutane'?

It is important to watch for the special symptoms listed above as these may be signs of serious side effects.

The side effects listed below are generally temporary and disappear when 'Accutane' treatment is stopped; however, you must tell your doctor if any of your side effects do not clear up in a few weeks after you stop taking 'Accutane'. **You must also check with your doctor, if these effects become bothersome, to see if any change in your medication is needed.**

- Some of the most common side effects are: dryness of the skin, lips, mouth, and lining of the nose. Some other side effects that may occur include: facial or body rash, flaking of the skin, itching, peeling of the palms and soles, increased sensitivity to the sun, inflammation of the

lips, mild nose bleed, bleeding and inflammation of the gums, easily injured skin and increased fatigue. You may experience some redness, dryness, or irritation of the eyes.

- If you wear contact lenses, you may find them uncomfortable during treatment because 'Accutane' may cause dry eyes. This may continue after treatment has stopped.
- In some patients variable amounts of hair loss have occurred. In rare cases, this hair loss persisted after treatment was completed.

These are not all of 'Accutane's' possible side effects. Your doctor or pharmacist can give you more detailed information that is written for health care professionals.

How should you take 'Accutane'?

- Keep 'Accutane' out of the reach of children.
- Read your prescription label carefully and be sure to take the exact amount of medicine prescribed by your doctor. Your doctor may change your prescribed dose from time to time, therefore, it is important that you check the label each time you fill your 'Accutane' prescription. If you have any questions, call your doctor.
- Take 'Accutane' with food or just after a meal. If you forget to take a dose of 'Accutane', it may be taken later the same day, but, do not take more 'Accutane' in one day than your doctor has prescribed.
- Be sure to return to your doctor as scheduled. It is important for your doctor to see you regularly, every month, when you are taking 'Accutane'. Blood tests and other tests allow your doctor to check your response to 'Accutane'. Discuss your progress and any concerns with your doctor.
- Protect 'Accutane' capsules from sunlight and heat. 'Accutane' does not need to be refrigerated.

What should you expect while taking 'Accutane'?

During the first few weeks of treatment, your acne may seem to get worse. Redness and itching of the affected skin are common initial effects. These should disappear as you continue to take 'Accutane'. Most often, the first signs of healing occur after two to three weeks of treatment. It may take one to two months before beneficial effects are seen. Most patients with severe acne notice a marked improvement after one or two courses of treatment with 'Accutane'.

Active Ingredient: Isotretinoin

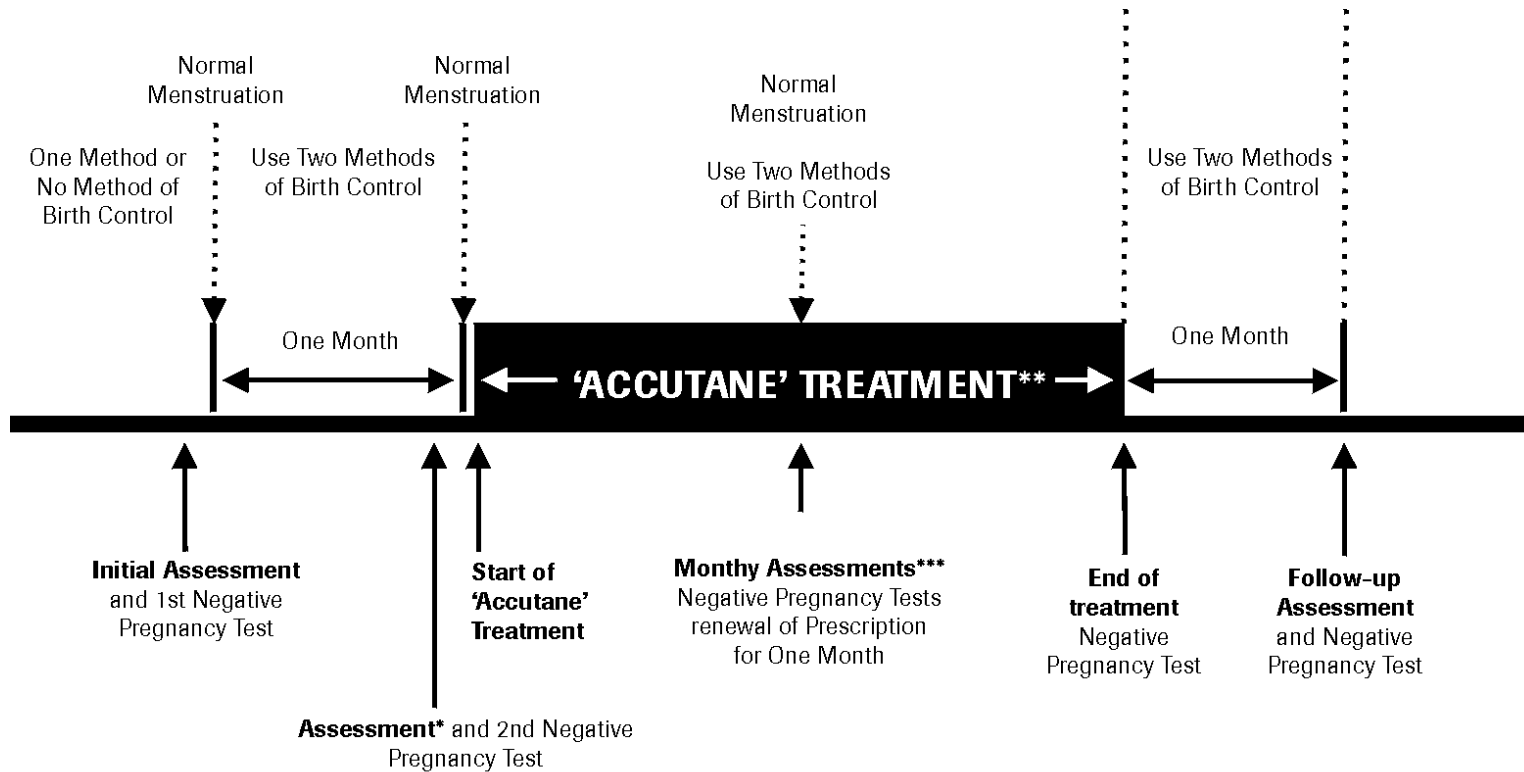
Inactive Ingredients

'Accutane' 'Roche' 10: beeswax, canthaxanthin, gelatin, glycerin, hydrogenated hydrolysed starch, mannitol, soybean and hydrogenated soybean oil, sorbitol, titanium dioxide.

'Accutane' 'Roche' 40: beeswax, gelatin, glycerin, methylparaben, propylparaben, quinoline yellow WS, soybean and hydrogenated soybean oil, sunset yellow FCF, titanium dioxide.

This Information for the Consumer is only a summary of some important information about 'Accutane'. Medicines are sometimes prescribed for purposes other than those listed in an Information for the Consumer. If you have any concerns or questions about 'Accutane', ask your doctor. Do not use 'Accutane' for a condition for which it was not prescribed.

'ACCUTANE' PREGNANCY PREVENTION PLAN



* To ensure that you are using two reliable methods of birth control at the same time.

** Duration of therapy is typically 3-4 months.

*** To ensure that you are using two reliable methods of birth control at the same time, and to detect any side effect that you may have from the treatment.

PHARMACOLOGY

Isotretinoin exerts a specific action on the sebaceous glands of the hamster flank organs. Subcutaneous administration of isotretinoin to female hamsters treated simultaneously with testosterone enanthate prevents the androgen-induced growth of flank organ sebaceous glands without affecting other androgen dependent cells (i.e. does not inhibit development of pigment or larger hair follicles).

Doses up to 300 mg/kg p.o. of isotretinoin have no effect upon circulation and respiratory parameters in the anesthetized cat. A dose of 1 g/kg results in respiratory stimulation and a slight decrease in blood pressure, pulse rate, blood flow to the extremities as well as oxygen saturation.

TOXICOLOGY

Acute Toxicity Studies:

Animal	Route	LD ₅₀	Observation Period
mouse	p.o.	3,389 mg/kg	--
mouse	i.p.	904 mg/kg	10, 20 days
rat	p.o.	> 4,000 mg/kg	14 days
rat	i.p.	901 mg/kg	10, 20 days
rabbit	p.o.	approx. 1,960 mg/kg	14 days

(signs and symptoms: sedation and respiratory depression)

Pyramiding doses of 4.8, 13.1, 41.2 and 79.8 mg/kg of isotretinoin were administered to dogs. All dogs survived. Diarrhea occurred in dogs treated with doses of 13.1 mg/kg or higher.

Long-Term Toxicity Studies:

55-week Oral Toxicity -Dog

In a 55-week toxicity study conducted in beagle dogs (9/sex/ group), isotretinoin was administered as a dietary admix at doses of 3, 20 or 120 mg/kg/day. Severe toxicity developed in the high-dose group and administration was stopped at the end of week 4. Isotretinoin was restarted in this group at the end of 12 weeks, but at a reduced dosage of 60 mg/kg/day. After 7 weeks, administration again had to be stopped for 6 weeks. Administration continued uninterrupted until week 30. Thereafter, the high-dose group was maintained on a cycle of 2 weeks no treatment followed by 6 weeks of treatment with 60 mg/kg/day.

In the high-dose group (60/120 mg/kg/day), the following toxic manifestations were observed: weight loss, skin lesions, visible blood in feces, ophthalmological changes (epiphora, superficial punctate corneal opacities in the subepithelial stroma, vascularization of the subepithelial corneal stroma and congestion or hyperemia of the palpebral and/or bulbar conjunctiva),

decreases in hematocrit and hemoglobin, decreased mean serum glucose levels, slight alterations in mean serum transaminase activity, elevations in mean serum alkaline phosphatase activity, and qualitative albuminuria.

Most clinical signs of toxicity disappeared or diminished when isotretinoin was withdrawn and reappeared when treatment was reactivated. Pathological changes in the high-dose group included: increased incidence of focal gross lesions in the gastrointestinal tract, testicular atrophy with evidence of spermatogenic arrest, increased mean liver weight, microscopic evidence for edema and/or erythrophago-cytosis of the lymph nodes, encephalomalacia limited to single microscopic foci in the brain of two dogs, and degeneration of elastic fibre in four dogs.

Many of the clinical and pathological signs, except for weight loss and corneal opacities, seen in the high dosage group were also evident in the dogs treated with 20 mg/kg/day. However, a tendency towards a decreased frequency and a longer time to first appearance than in the high-dose group was noted.

The low dosage (3 mg/kg/day) was well tolerated, but microscopic changes in the lymph nodes were observed in the same number of dogs as was recorded for the mid-dose group.

Two-year Oral Toxicity - Rat

Isotretinoin was administered to rats (80/sex/group) as a dietary admix for two years. All groups received 1 mg/kg/day for 13 weeks in order to avoid excessive bone fractures during the major period of growth. Thereafter, doses of 2, 8 and 32 mg/kg/day were administered. In the high-dose group, administration of drug was discontinued during weeks 29-41 and 67-73 due to long bone fracture.

32 mg/kg/day

Upon completion of the study, the following clinical and laboratory findings were observed in the high dose group: increased mortality, decreased body weight gain and food consumption; altered gait (related to possible long bone fracture); decreased hemoglobin and hematocrit; elevated serum alkaline phosphatase, serum triglycerides, serum phosphate, and serum urea nitrogen; exacerbated age- and sialodacryoadenitis (SDA) virus-related eye changes; skin lesions; some increased organ weights. The following histopathological findings were noted: reduplication of small bile ducts; focal fibrosis and focal chronic inflammation of the heart; focal dilation of renal tubules and focal chronic inflammation of the kidney; adrenal medullary lesions (hyperplasia and pheochromocytomas); arteritis; calcification of arteries; focal calcification in tissues; focal osteolysis of bone.

8 mg/kg/day

When isotretinoin was administered to rats at 8 mg/kg/day as a dietary admix for two years, the clinical and laboratory findings were: increased mortality; decreased body weight gain; decreased hemoglobin and hematocrit; elevated serum alkaline phosphatase and serum triglycerides; exacerbated age- and SDA virus-related eye changes; skin lesions; some increased organ weights. The histopathological findings were: reduplication of small bile ducts; focal fibrosis and focal chronic inflammation in the heart; renal tubular dilation and focal chronic inflammation in the kidney; adrenal medullary lesions (hyperplasia and pheochromocytomas); arteritis; calcification of arteries; focal calcification in tissues; focal osteolysis of bone.

2 mg/kg/day

When isotretinoin was administered to rats at 2 mg/kg/day as a dietary admix for two years, the clinical and laboratory findings were: elevated serum alkaline phosphatase values, some increased organ weights. The histopathological findings were: reduplication of small bile ducts; increased focal chronic inflammation of the kidneys; arteritis; calcification of arteries; focal calcification in tissues.

Although an increased incidence of pheochromocytomas and adrenal medullary hyperplasia were observed at the high and mid doses, no increase was observed at the low dose. It is very likely that this increase in number of adrenal medullary proliferative lesions was mediated by an effect upon hormonal status in rats that were already hormonally abnormal because of their genetic origin and overfeeding, as well as other aspects of the environment of laboratory rats. Dose-related decreases in the incidence of liver adenomas and angiomas in male rats and leukemia in female rats were also noted.

Reproduction and Teratology Studies:

Fertility and General Reproductive Performance -Rat

Isotretinoin at doses of 2, 8 or 32 mg/kg/day was administered orally to male rats for 63 days prior to mating and through the mating period and to females for 14 days prior to mating and through day 13 of gestation or day 21 of gestation or day 21 of lactation. No adverse effects on fertility and general reproductive performance was observed except for a slight reduction in the weight of weanlings in the high-dose group.

Teratology - Rat

A teratology study was conducted in rats with 5, 15 or 50 mg/kg/day of isotretinoin administered orally on gestation days 7 through 15. Doses of up to 50 mg/kg/day of isotretinoin were found to be nonteratogenic. In an earlier study a dose of 150 mg/kg/day was observed to be teratogenic.

Teratology - Rabbit

New Zealand white rabbits were administered isotretinoin at doses of 1, 3 or 10 mg/kg/day on days 7 through 18 of gestation. No teratogenic or embryotoxic effects were observed at 1 and 3 mg/kg/day. At 10 mg/kg/day, 9/13 does aborted and teratogenicity and embryotoxicity were observed in the remaining four litters.

Perinatal and Postnatal Evaluation - Rat

Rats were administered isotretinoin at doses of 5, 15 or 32 mg/kg/day orally from gestation day 14 through day 21 of lactation. Increased pup mortality, considered secondary to reduced maternal food intake, was noted in all treated groups and particularly in the high-dose group. Body weight development of pups was impaired significantly in the high-dose group. Similarly, this effect was considered due to a reduced food intake by the dams.

Mutagenicity Testing

Isotretinoin was non-mutagenic in the Ames Test at concentrations up to 2 mg per plate in the absence or presence of metabolic activation.

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