

PRODUCT MONOGRAPH

Pr ACCUTANE™ ROCHE®

Isotretinoin capules USP, 10, 40mg

Nodular/Inflammatory and Conglobate Acne Therapy

Hoffmann- La Roche Limited
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Mississauga, Ontario
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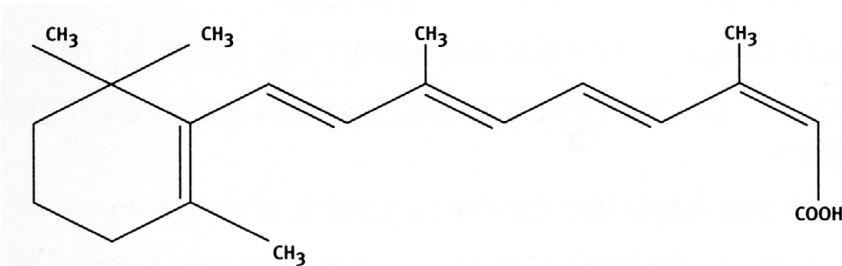
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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Isotretinoin
Chemical Name:	3-7-dimethyl-9-(2,6,6-trimethyl-1-cyclo-hexen-1-yl)-2,4,6,8- nonatetraenoic acid
Molecular Formula:	C ₂₀ H ₂₈ O ₂
Molecular Weight:	300.44
Structural Formula:	

Physiochemical properties:

Orange crystalline powder, insoluble in water; soluble in chloroform (10g / 100 mL). Melting point approximately 175°C; pKa approximately 4.

DETAILED 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 orally 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	oral	3,389 mg/kg	--
mouse	intraperitoneal	904 mg/kg	10, 20 days
rat	oral	> 4,000 mg/kg	14 days
rat	intraperitoneal	901 mg/kg	10, 20 days
rabbit	oral	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.

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.

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:

Like other Vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic; however, there is a large species variation in the teratogenic effect. Rats have been reported to be less sensitive to the teratogenic effects of isotretinoin; whereas, humans have been reported to be the most sensitive. Differences in sensitivity are a result of interspecies differences in the pharmacokinetics and placental transfer of isotretinoin.

The following table provides the low dose (mg/kg) reported to elicit teratogenesis in animal models.

Species	Low dose to elicit teratogenic effect
Mouse/rat	75-150 mg/kg
Rabbit	10 mg/kg
Monkey	2.5-5 mg/kg
Human	0.4-1 mg/kg

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 were 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. Isotretinoin has not been shown to be mutagenic or carcinogenic in *in vitro* or *in vivo* animal tests, respectively.

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