STUDY PROTOCOL COVER PAGE

Official Title: Randomised Controlled Trial of Two Different Cumulative Dosages of Roaccutane for Cystic Acne

Short Title: Roaccutane 120 mg/kg vs 150 mg/kg for Cystic Acne

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Study Identifier (NCT Number): To be assigned by ClinicalTrials.gov upon registration

Date: 23 June 2005

PROTOCOL

RANDOMISED CONTROLLED TRIAL OF TWO DIFFERENT CUMULATIVE DOSAGES OF ROACCUTANE FOR CYSTIC ACNE

Objective: Comparison of the effectiveness of Roaccutane at total cumulative dosages of 120 mg/kg vs 150 mg/kg.

Clinical Hypothesis: A 150 mg/kg cumulative dosage regimen is more effective at treating acne vulgaris and the presence of a remission from the disorder than 120 mg/kg.

Methodology: The study will be a multicenter, controlled, randomized study.

Number of subjects: It has been determined that to detect a 10% difference between the two dosage schedules of Roaccutane which are being tested (120mg/kg vs 150mg/kg) 450 subjects will be required with 225 in each group.

Diagnosis and Main Inclusion Criteria: Male or Female subjects, of any age, of any race, with a clinical diagnosis of nodulo-cystic acne as well as patients who have been unresponsive to standard acne vulgaris treatments.

Exclusion Criteria: pregnant or lactating female patients, female patients with polycystic ovarian syndrome, insulin resistance syndrome, previous use of Roaccutane, patients with congenital adrenal hyperplasia, patients with any internal malignancy (excluding skin cancer); females of reproductive potential who refuse to take the oral contraceptive pill to take roaacutane; patients who in the investigator's opinion would be unlikely to be compliant.

Investigational Product: Roaccutane 20mg tablets 150mg/kg total dose

Comparator Product: Roaccutane 20mg tablets 120mg/kg total dose

Study Duration/Visits: Visits include before treatment initiation, and at least every two months thereafter, including when the 120mg/kg dose and at 150mg/kg cumulative doses are reached. The patients are assessed 3 months after finishing roaccutane and at one year after roaccutane treatment has ceased to record response and recurrence rates.

Criteria for Evaluation: Acne lesion counts will consist of counting specifically white heads, blackheads, papules, pustules, nodules, deep pustules measured on both the left and right sides of the face, the same lesions will be measured on the chest and on the back. Scarring assessments will be done in terms of icepick scars, macular atrophic scars, follicular macular atrophic scars, hypertrophic/keloid scars and peri-follicular papular scars on the face, chest and back. An acne grade will also be assigned which ranges from 1 - 8. This acne grade has been established in the article *"Predictive*

factors for failure of isotretinoin treatment in acne patients; results from a cohort of 237 patients", Dermatology 1999;198: 278-283.

Other methods of note:

1. For consistency, all female patients of child bearing potential will be asked to use an oral contraceptive pill. A second form of contraception will be required.

2. Standard investigations for this study to identify potential factors include two negative serum pregnancy tests immediately before starting on treatment,, testosterone level, sex hormone binding globulin, luteinizing hormone level, follicle stimulating hormone level, androstenedione level, 17 hydroxy-progesterone level and glucose tolerance tests. Transabdominal and/or transvaginal ovarian ultrasound when appropriate.

3. Other laboratory tests will be drawn before starting roaccutane including a full blood count,UEC, lipid panel, and liver function tests.

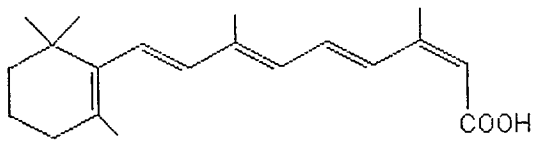
4. Once the decision to start Roaccutane has been taken, patients will be randomised to either treatment group that being 120mg/kg or 150mg/kg cumulative dose. If the patient's acne is still active during the month they are due to cease treatment their course of treatment will be continued.

5. Before commencing on either Roaccutane dose a study consent form, which has been approved by the SESIAHS Ethics Committee,

6. Separate forms are available for minors.

NAME OF THE DRUG

ROACCUTANE
(isotretinoin)
CAS 4759-48-2



13-cis-Retinoic Acid

Chemically, isotretinoin is (2*Z*, 4*E*, 6*E*, 8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid and is also known as 13-cis-retinoic acid. Isotretinoin is related to both retinoic acid and retinol (vitamin A). The molecular formula is $C_{20}H_{28}O_2$. Isotretinoin has a molecular weight of 300.44.

DESCRIPTION

Isotretinoin is a yellow orange to orange crystalline powder, practically insoluble in water, soluble in methylene chloride, sparingly soluble in ether and slightly soluble in alcohol. It is sensitive to air, heat and light, especially in solution.

ROACCUTANE is available in 10 and 20 mg soft gelatin capsules for oral administration. In addition to isotretinoin, the capsules contain soya oil, yellow beeswax , hydrogenated vegetable oil and hydrogenated soya oil.

The capsule shell contains gelatin, glycerol, purified water, titanium dioxide , canthaxanthin CI40850 and proprietary ingredient Karion 83 (by R.P. Scherer GmbH, ARTG No. 2072).

The printing ink, black ink edible A-R-10379 (ARTG No. 2268) contains shellac and iron oxide black CI77499.

PHARMACOLOGY

Pharmacodynamics

Isotretinoin is a retinoid that inhibits sebaceous gland function and keratinisation. The exact mechanism of action of ROACCUTANE is unknown.

Clinical improvement in cystic acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is reversible and the extent is related to the dose and duration of treatment with ROACCUTANE and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

Pharmacokinetics

Absorption
There is considerable inter-individual variation in the bioavailability of oral isotretinoin. After oral administration of 80 mg (2 x 40 mg capsules) given in the fasting state peak plasma concentrations ranged from 167 to 459 nanogram/mL and mean time to peak was 3.2 hours in healthy volunteers, while in acne patients peak concentrations ranged from 98 to 535 nanogram/mL (mean 262 nanogram/mL) with a mean time to peak of 2.9 hours.

The bioavailability of ROACCUTANE capsules taken with food is 1½ to 2 times greater than when taken in a fasting state.

Distribution
Tissue Distribution in Animals: Tissue distribution of ^{14}C- isotretinoin in rats revealed high concentrations of radioactivity in many tissues after 15 minutes, with a maximum in 1 hour, and declining to non-detectable levels by 24 hours in most tissues. After seven days, however, low levels of radioactivity were detected in the liver, ureter, adrenal, ovary and lacrimal gland.

The drug is 99.9% bound in human plasma almost exclusively to albumin.

Metabolism
The major identified metabolite in blood and urine is 4-oxo-isotretinoin. Tretinoin and 4-oxo-tretinoin were also observed. After two 40 mg capsules of isotretinoin, maximum concentrations of the metabolite of 87 to 399 nanogram/mL occurred at 6 to 20 hours. The blood concentration of the major metabolite generally exceeded that of isotretinoin after 6 hours.

The mean $\pm$SD minimum steady-state blood concentrations of isotretinoin were 160 $\pm$19 nanogram/mL in 10 patients receiving 40 mg twice daily. After single and multiple doses, the mean ratio of areas under the curves of isotretinoin to 4-oxo-isotretinoin is 3 to 3.5.

Excretion
The terminal elimination half-life of isotretinoin ranged from 10 to 20 hours in volunteers and patients. Following an 80 mg liquid suspension oral dose of ^{14}C-isotretinoin, ^{14}C-activity in blood declined with a half-life of 90 hours. Relatively equal amounts of radioactivity were recovered in the urine and faeces with 65-83% of the dose recovered. The apparent half-life for elimination of the 4-oxo-metabolite ranged from 11 to 50 hours with a mean of 29 hours. This metabolite is subject to recycling in the enterohepatic circulation.

INDICATIONS

ROACCUTANE is indicated for the treatment of severe cystic acne, and a single course of therapy has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least eight weeks after completion of the first course, since experience has shown that patients may continue to improve while off drug. Because of significant adverse effects associated with its use, ROACCUTANE should be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including systemic antibiotics.

CONTRAINDICATIONS

Use in Pregnancy (Category X): ROACCUTANE must not be used by females who are pregnant or who may possibly become pregnant while undergoing treatment.

Major human fetal abnormalities related to ROACCUTANE administration have been reported, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), eye abnormalities (including microphthalmia), cardiovascular abnormalities, facial dysmorphia, cleft palate, thymus gland abnormality, parathyroid gland abnormalities and cerebellar malformation.

Women of childbearing potential should not be given ROACCUTANE until pregnancy is excluded. It is strongly recommended that a pregnancy test be performed within two weeks prior to ROACCUTANE therapy. ROACCUTANE therapy should start on the second or third day of the next normal menstrual period. An effective form of contraception should be used for at least one month before and also throughout ROACCUTANE therapy.

It is recommended that contraception be continued for one month following discontinuation of ROACCUTANE therapy. Females should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

ROACCUTANE is contraindicated in patients who are breast- feeding (see PRECAUTIONS – USE IN LACTATION).

ROACCUTANE is contraindicated in patients with severely impaired liver function and in patients with chronic abnormally elevated blood lipid values.

ROACCUTANE is also contraindicated in people who are hypersensitive to the drug or other ingredients in ROACCUTANE capsules or to other retinoids.

ROACCUTANE is contraindicated in patients who have pre-existing hypervitaminosis A.

Rare cases of benign intracranial hypertension have been reported after ROACCUTANE and after tetracyclines. Concomitant treatment with tetracyclines is therefore contraindicated. (See also **PRECAUTIONS: Interactions with Other Drugs**).

PRECAUTIONS

Information for patients

Women of childbearing potential should be warned that the drug causes birth defects. They should be instructed that they must not be pregnant when ROACCUTANE therapy is initiated, and that they should use an effective form of contraception while taking ROACCUTANE and for one month after ROACCUTANE has been stopped. (See CONTRAINDICATIONS).

Patients should be informed that transient exacerbation of acne has been seen, generally during the initial period of therapy.

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

Donation of blood by patients during and within one month of cessation of ROACCUTANE treatment to women of childbearing potential should be avoided.

Wax epilation should be avoided in patients on ROACCUTANE and for a period of 5-6 months after treatment because of risk of scarring or dermatitis.

Dermabrasion should be avoided in patients on ROACCUTANE and for a period of 5-6 months after treatment because of risk of hypertrophic scarring in atypical areas.

Pseudotumour cerebri
ROACCUTANE use has been associated with a number of cases of pseudotumour cerebri (benign intracranial hypertension), some of which involved the concomitant use of tetracyclines. Early signs and symptoms of pseudotumour cerebri include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilloedema and, if present, they should be told to discontinue ROACCUTANE immediately and be referred to a neurologist for further diagnosis and care.

Visual Abnormalities
Corneal opacities have occurred in patients receiving ROACCUTANE for acne and more frequently when higher drug dosages were used in patients with disorders of keratinisation. All ROACCUTANE patients experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

A number of cases of decreased night vision have occurred during ROACCUTANE therapy. As 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.

Dry eyes, corneal opacities, conjunctivitis, blepharitis, intolerance to contact lenses, decreased night vision and keratitis usually resolve after discontinuation of 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 ROACCUTANE considered.

Biochemical Abnormalities
Rises in alanine and aspartate aminotransferase enzymes (ALT and AST) have been reported. Liver function tests, especially AST and blood lipids should be measured before therapy and at monthly intervals during therapy and at the end of treatment. When transaminase levels exceed the normal levels, reduction of the dose or discontinuation of treatment may be necessary.

Isotretinoin causes elevation of serum triglycerides and cholesterol as well as a decrease in H.D.L., which appear to be related to duration of treatment and are reversible on cessation of treatment. The degree of elevation may also be dose dependent although this has not been conclusively established.

At doses of greater than 1 mg/kg/day, approximately one in four patients has been found to develop elevated triglycerides while taking ROACCUTANE. At lower doses triglyceride levels elevated above the normal range are uncommon.

Acute pancreatitis, which is potentially fatal, sometimes associated with serum triglycerides levels >8g/L, has been reported. Hence, ROACCUTANE should be discontinued if uncontrolled hypertriglyceridemia or symptoms of pancreatitis occur.

Predisposing factors such as a family history of lipid disorders, obesity, alcohol abuse, diabetes and smoking should be assessed. Serum lipid should be determined prior to therapy and again after about 4 weeks, and subsequently at three month intervals unless more frequent monitoring is clinically indicated.

Some patients have been able to reverse triglyceride elevations by weight reduction and restriction of dietary fat and alcohol while continuing to take ROACCUTANE. Serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment.

In high risk patients (with diabetes, obesity, alcoholism or lipid metabolism disorder) undergoing treatment with ROACCUTANE, more frequent checks of serum values for lipids and/or blood glucose may be necessary.

Hyperostosis
In clinical trials of disorders of keratinisation with a mean dose of 2.24 mg/kg/day a high prevalence of skeletal hyperostosis was noted. Bone changes including premature epiphyseal closure have occurred after administration of high doses for long periods for treating disorders of keratinisation.

Minimal skeletal hyperostosis has also been observed by X-rays in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses.

Due to the possible occurrence of these bone changes, a careful evaluation of the risk/benefit ratio should be carried out in every patient and ROACCUTANE administration should be restricted to severe cases.

Hepatotoxicity
Several cases of clinical hepatitis have been noted which are considered to be possibly or probably related to ROACCUTANE therapy. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalised with dosage reduction or continued administration of the drug. If normalisation does not readily occur or if hepatitis is suspected during treatment with ROACCUTANE, the drug should be discontinued and the etiology further investigated.

Psychiatric disorders
Depression, psychosis and, rarely, suicidal ideation and attempts have been reported with ROACCUTANE. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression. Although no mechanism of action for these events has been established, discontinuation of therapy may be insufficient and further evaluation by a psychiatrist may be necessary.

Inflammatory bowel disease
ROACCUTANE has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing abdominal pain, rectal bleeding or severe (hemorrhagic) diarrhea should discontinue ROACCUTANE immediately.

Anaphylactic reactions
These have been reported rarely and only after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. 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.

Renal Impairment
ROACCUTANE should be started at a lower dose in patients with severe renal insufficiency and afterwards dose adjusted according to tolerance.

Exercise Tolerance
Myalgia and arthralgia may occur and may be associated with reduced tolerance to vigorous exercise (see **Adverse Reactions**). Isolated instances of raised CPK levels have been reported in patients receiving ROACCUTANE, particularly those undergoing vigorous physical activity.

Carcinogenesis, Mutagenesis and Impairment of Fertility
In Fischer 344 rats given isotretinoin at dosages of 32 or 8 mg/kg/day for greater than 18 months, there was dose-related increased incidence of pheochromocytoma. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage. There is doubt as to the validity of this animal model as a predictor of tumorigenicity in man, as the Fischer rat is genetically predisposed to the Multiple Endocrine Neoplasia Syndrome which includes spontaneous occurrence of pheochromocytoma. In these studies there was also a dose-related decrease in the incidence of liver adenomata, liver angiomata and leukemia.

Isotretinoin was negative in tests for gene mutation (histidine reversion in *S. typhimurium)*, chromosomal damage *in vitro* (Chinese hamster lung cell and *S. cervisiae D7 assays) and in vivo* (Mouse micronucleus test), and unscheduled DNA synthesis *in vitro* (rat hepatocytes).

In the reproductive studies in rats (2, 8 or 32 mg/kg/day; 2-generation), no adverse effects were noted on gonadal function, fertility, gestation or neonatal viability, although the average weight in the high dose group was slightly reduced.

In dogs, testicular atrophy was noted after treatment with isotretinoin for approximately 30 weeks at dosages of 60 or 20 mg/kg/day. In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies in 66 human males, 30 of who were patients with cystic acne, no significant changes were noted in the count or motility of spermatozoa in the ejaculate.

Use in Pregnancy
Pregnancy Category X

Isotretinoin is a known human teratogen and should not under any circumstances be administered during pregnancy. For more details see under **CONTRAINDICATIONS**.

ROACCUTANE should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity.

Isotretinoin is teratogenic in rats and rabbits although sensitivity differs. In the rat, doses up to 50 mg/kg/day were not teratogenic but 150 mg/kg/day was teratogenic. At lower doses in the rat perinatal and post-natal studies (5, 15 and 32 mg/kg/day) increased pup mortality was noted in all treatment groups. This was attributed to a dose-related reduction in maternal food intake. Body weight development of pups was significantly impaired in the high dose groups.

In the rabbit, a dose of 10 mg/kg/day caused abortions in 9 out of 13 animals and teratogenicity and embryotoxicity were observed in the remaining 4 litters.

Use in Lactation
As isotretinoin is highly lipophilic, the passage of the drug in human milk is very likely. Because of the potential for adverse effects, breastfeeding mothers should not receive ROACCUTANE.

Use in Children
The approved therapeutic indication does not involve use in children and safety in prepubertal children has not been established. (See also PRECAUTIONS: Hyperostosis).

Interactions with Other Drugs
As a rule concomitant therapy is not indicated but non-irritant topical preparations may be used if required.

Concurrent treatment with Vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified (see **ADVERSE REACTIONS**).

Cases of pseudotumour cerebri and/or papilloedema have been reported in association with the use of isotretinoin. Four out of ten of these patients had retinal hemorrhages. Symptoms appeared after 21 days to 6 months therapy with 40 to 120 mg daily. Concomitant tetracycline or minocycline was administered in 5 out of 10 cases - both of these drugs have been implicated in causing intracranial hypertension. Concomitant therapy with tetracyclines is contraindicated. (See under **CONTRAINDICATIONS**).

Since acne is an androgen-dependent disease, contraceptives containing an androgen progestational substance, such as one derived from 19-nortestosterone (norsteroid), particularly in the presence of gynaeco-endocrinological problems, should be avoided.

The effect of microdosed progesterone preparations may be diminished by interaction with isotretinoin. Therefore, microdosed progesterone preparations or 'minipills' should not be used.

Effects on Laboratory Tests
Elevation of lipid (triglycerides and cholesterol) levels occurs with ROACCUTANE therapy. These are usually mild in doses less than 1 mg/kg/day and elevations above the normal range are unusual at 0.5 mg/kg/day. At doses above 1 mg/kg/day, elevation (above the normal range) occurs in 25% of patients.

These changes are seen more frequently in patients where a family history of lipid disorders, or obesity, alcohol abuse, diabetes mellitus or smoking is present. The changes are dose related and may be controlled by dietary means (including alcohol restriction) or dosage reduction. (See also **PRECAUTIONS: Biochemical Abnormalities**).

Elevated ESR values occur in about 40% of patients treated with ROACCUTANE.

A rise in aspartate aminotransferase (AST) levels may occur, especially with the higher dosages of ROACCUTANE. 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 ROACCUTANE.
Certain patients receiving ROACCUTANE have experienced problems in the control of their blood sugar. Therefore, known or suspected diabetics should have frequent blood sugar determinations performed during ROACCUTANE therapy. New cases of diabetes have been diagnosed.

A small number of patients have shown proteinuria, microscopic or gross hematuria and elevated CPK.

ADVERSE REACTIONS

Most adverse effects appear to be dose related with the more pronounced effects occurring at doses above 1 mg/kg/day. The adverse effects may recede during continued therapy and the mucocutaneous effects were reversible with dosage reduction or discontinuation of therapy. Exacerbation of the cystic acne may occur during the initial stages of therapy.

Post-Marketing Experience

Symptoms associated with hypervitaminosis A
The most common side effects are mucocutaneous. The most frequently reported effects are dryness of the skin, in particular peeling of the palms and soles, dryness of the mucosa eg of the lips (cheilitis, which occurs in over 90% of patients), the nasal mucosa (epistaxis, which is seen in up to 30% of patients), the pharynx (hoarseness), the eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).

Skin and 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.

Musculoskeletal system disorders
Myalgia (muscle pain) with or without elevated serum CPK values (see **PRECAUTIONS**), arthralgia (joint pain), hyperostosis, arthritis, calcification of ligaments and tendons and other bone changes, tendinitis.

Psychiatric and central nervous system disorders
Behavioural disorders, depression (see **PRECAUTIONS**), headache, increased intracranial pressure (pseudotumour cerebri), seizures.

Sensory disorders
Visual disturbances, photophobia, decreased night vision, colour vision disturbances, lenticular cataracts, keratitis, impaired hearing at certain frequencies.

Gastrointestinal system disorders
Nausea, inflammatory bowel disease such as colitis, ileitis, and hemorrhage have been reported to occur. Patients treated with ROACCUTANE, especially those with high triglyceride levels are at risk of developing pancreatitis. Fatal pancreatitis has been rarely reported (see **PRECAUTIONS**).

Liver and biliary system disorders
Transitory and reversible increases in liver transaminases, some cases of hepatitis.

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

Disorders of the blood

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

Laboratory Findings

Increase in serum triglyceride 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 **PRECAUTIONS**).

Resistance Mechanism Disorders

Local or systemic infections due to Gram positive microorganisms (*Staphylococcus aureus*).

Miscellaneous Reactions

Decreases in hematocrit, lymphadenopathy, hematuria, and proteinuria, vasculitis (for example Wegener's granulomatosis, allergic vasculitis), allergic responses, systemic hypersensitivity, glomerulonephritis.

DOSAGE AND ADMINISTRATION

The therapeutic response to ROACCUTANE 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 16 week course of treatment.

All patients initially should receive ROACCUTANE at doses up to 0.5 mg/kg/day bodyweight 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. Satisfactory initial responses have been reported from 0.05 mg/kg/day. Relapse rates on the lower doses are higher (a second course may be required in about two-thirds of patients on 0.1 mg/kg/day for 16 weeks), but there is decreased incidence and severity of adverse reactions at lower doses.

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.

Doses up to 1 mg/kg/day may be used in patients refractory to initial treatment at lower doses.

The above daily dosages of ROACCUTANE should be continued for 16 weeks to complete the course of treatment.

After a period of two months off therapy, and if warranted by persistent severe cystic acne, a second course of therapy may be initiated.

OVERDOSAGE

Clinically, overdose has been associated with transient headache, vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness and ataxia. All symptoms quickly resolved without apparent residual effects.

The oral LD_{50} of ROACCUTANE is greater than 4000 mg/kg in rats and mice and approximately 1960 mg/kg in rabbits.

PRESENTATION

Soft gelatin capsules
10 mg x 60 capsules, reddish-violet in colour, oval shaped, imprinted with ROA 10.
20 mg x 60 capsules, reddish-violet in colour one half, white opaque the other half, oval shaped, imprinted with ROA 20.

SPONSOR

Roche Products Pty. Limited
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