

AUSTRALIAN PRODUCT INFORMATION

Roaccutane (isotretinoin)

1. NAME OF THE MEDICINE

Isotretinoin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Roaccutane 20 mg capsule contains isotretinoin 20mg

Excipients with known effect

Contains soya bean oil (refined, hydrogenated and partially hydrogenated).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Roaccutane 20 mg - half brown-red soft capsule half opaque white, imprinted with ROA 20

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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.

4.3 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 (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), facial dysmorphism, cleft palate, thymus gland abnormality, parathyroid gland abnormalities and cerebellar malformation/abnormalities. There is also an increased incidence of spontaneous abortion.

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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

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 section 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Roaccutane is also contraindicated in people who are hypersensitive to the drug or other ingredients in Roaccutane capsules listed in section 6.1 LIST OF EXCIPIENTS or to other retinoids.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 section 4.3 CONTRAINDICATIONS).

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.

Roaccutane contains soya oil therefore caution should be taken with patients allergic to peanut or soya.

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

Skin and Subcutaneous Tissue Disorders

Acute exacerbation of acne is generally seen during the initial period of treatment; but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustments.

Wax epilation should be avoided in patients on Roaccutane and for a period of 5 to 6 months after treatment because of risk of epidermal stripping, scarring or dermatitis.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on Roaccutane and for a period of 5-6 months after the end of treatment because of risk of hypertrophic scarring in atypical areas and more rarely hyper- or hypo-pigmentation in treated areas.

Exposure to intense sunlight or UV rays should be avoided. Where necessary, a sun protection product with a high protection factor of at least SPF 15 should be used.

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

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

Benign Intracranial Hypertension

Roaccutane use has been associated with a number of cases of benign intracranial hypertension (pseudotumour cerebri), some of which involved the concomitant use of tetracyclines. Early signs and symptoms of benign intracranial hypertension include papilloedema, headache, nausea and vomiting, and visual disturbances. Patients who develop benign intracranial hypertension should discontinue Roaccutane immediately.

Eye Disorders

Dry eyes, corneal opacities, conjunctivitis, blepharitis, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Due to the possible occurrence of keratitis, patients with dry eyes should be monitored. Patients experiencing visual difficulties should be referred for an expert ophthalmological examination and withdrawal of Roaccutane considered. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

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.

Hearing Impairment

Impaired hearing has been reported in patients taking Roaccutane. Hearing impairment can be unilateral or bilateral, and symptoms include tinnitus, impaired hearing at certain frequencies and deafness. In some cases, hearing impairment has been reported to persist after therapy has been discontinued. Anyone who experiences these symptoms should immediately seek medical advice; the drug should be ceased and the patient should undergo urgent formal audiology assessment.

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 have been found to develop elevated triglycerides while taking Roaccutane. At lower doses triglyceride levels elevated above the normal range are uncommon.

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.

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.

Serum lipids (fasting value) should be determined one month prior to therapy and again after about 4 weeks of therapy and subsequently at three month intervals unless more frequent monitoring is clinically indicated.

Predisposing factors such as a family history of lipid metabolism disorders, obesity, alcoholism, diabetes and smoking should be assessed. 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.

Musculo-skeletal and Connective Tissue Disorders

Myalgia, arthralgia and increased serum creatine phosphokinase may occur and may be associated with reduced tolerance to vigorous exercise (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 and calcifications of tendons and ligaments have occurred after administration of high doses for long periods for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

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.

Roaccutane may be associated with growth retardation in prepubertal children.

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.

Use in Hepatic Impairment

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, psychotic symptoms, and, rarely, suicide, 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 Roaccutane may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Gastrointestinal Disorders

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.

Allergic Reactions

Anaphylactic reactions have been rarely reported 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.

Use in Renal Impairment

Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, Roaccutane can be given to patients with renal insufficiency. Roaccutane should be started at a lower dose in patients with severe renal insufficiency and afterwards dose adjusted according to tolerance.

Paediatric Use

The approved therapeutic indication does not involve use in children and safety in prepubertal children has not been established. (See also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The use of Roaccutane in paediatric patients less than 12 years of age is not recommended.

Roaccutane may stop long bone growth in children who are still growing. The use of Roaccutane for the treatment of severe cystic acne in paediatric patients aged 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists.

Use in the Elderly

No data available.

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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

As a rule concomitant therapy is not indicated but non-irritant topical preparations may be used if required. Concurrent administration of Roaccutane with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.

Concurrent treatment with Vitamin A must be avoided, as symptoms of hypervitaminosis A may be intensified (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 section 4.3 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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 section 4.3CONTRAINDICATIONS.

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, the use of Roaccutane is contraindicated in breast-feeding mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Decreased night vision has occurred during Roaccutane therapy and in rare instances has persisted after discontinuation of 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Many of the adverse effects seen in patients receiving Roaccutane are similar to those described in patients taking very high doses of vitamin A.

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 e.g. 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.

During the post-marketing period, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with Roaccutane (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Musculoskeletal system disorders

Myalgia (muscle pain) with or without elevated serum CPK values (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), arthralgia (joint pain), hyperostosis, arthritis, calcification of ligaments and tendons and other bone changes, reduced bone density, back pain, epiphyses, premature fusion, tendinitis.

Serious cases of rhabdomyolysis, often leading to hospitalization and some with fatal outcome have been reported, particularly in those undertaking vigorous physical activity.

Psychiatric and central nervous system disorders

Behavioural disorders, depression, suicide attempt, suicide, (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), headache, increased intracranial pressure (pseudotumour cerebri), seizures.

Sensory disorders

Visual disturbances, photophobia, decreased night vision, colour vision disturbances (reversible upon discontinuation), lenticular cataracts, keratitis, blurred vision, blepharitis, conjunctivitis, eye irritation, papilledema as a sign of intracranial hypertension, impaired hearing at certain frequencies.

Gastrointestinal system disorders

Nausea, severe diarrhea, 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Liver and biliary system disorders

Transient 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.

Reproductive system and breast disorders

Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia. A causal association with these adverse effects has not been established.

Disorders of the blood

Decrease in white blood cell count, neutropenia, 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 (thrombocytopenia), anaemia.

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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs of hypervitaminosis A could appear in cases of overdose. 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.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Retinoid for treatment of acne, ATC code: D10B A01

Mechanism of Action

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

Pharmacodynamic effect

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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 ¹⁴C- 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.

Elimination

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 ¹⁴C-isotretinoin, ¹⁴C-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.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

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.

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule filling

Soya oil

Yellow beeswax

Partially hydrogenated soya oil

Hydrogenated soya oil.

Capsule shell

Gelatin

Glycerol

Titanium dioxide (CI77891)

Iron oxide red (CI77491)

Karion 83 (by R.P. Scherer GmbH, ARTG No. 2072).

Printing ink

Black ink edible S-1-27794 (ARTG No. 12104) which contains shellac and iron oxide black CI77499.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 degrees Celsius.

Protect from Light

6.5 NATURE AND CONTENTS OF CONTAINER

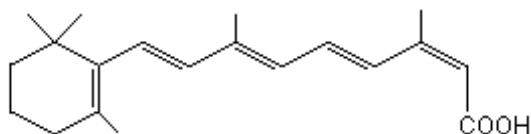
Roaccutane 20 mg is available in a blister pack of 30 or 60 capsules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



13-cis-Retinoic Acid

CAS number

4759-48-2

Chemically, isotretinoin is (2Z, 4E, 6E, 8E)-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 C₂₀H₂₈O₂. Isotretinoin has a molecular weight of 300.44.

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.

7. MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4 – Prescription only medicine

8. SPONSOR

Roche Products Pty Limited

ABN 70 000 132 865

Level 8, 30 – 34 Hickson Road

Roaccutane® PI 190415

Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

5 December 1994

10. DATE OF REVISION

13 May 2019

Summary of Changes Table

Section Changed	Summary of new information
4.8	Update to Post-Marketing Experience section to include <i>Reproductive system and breast disorders</i> .