



Roaccutane (Isotretinoin)

Roaccutane (Isotretinoin or 13-cis retinoic acid) is a very effective medication for the treatment of acne. It is a retinoid; this means it is derived from vitamin-A (retinoic acid). The liver naturally makes small quantities of Roaccutane from vitamin-A, but the drug we prescribe is made synthetically.

Roaccutane has been available since 1882. In Ireland Roaccutane is available as 5 mg and 20 mg capsules. In other countries, there are other brands of Roaccutane including Accutane® and Oratane®.

Most people receive a course of Roaccutane for 16 to 30 weeks (4 to 7 months), but some require it for longer. If necessary, it can be prescribed for children as well as adults.

If you are prescribed Roaccutane it is very important you read and understand about the medication. Ask your dermatologist to explain anything you do not understand.

Do not give your medication to anyone else. Do not start the medication if you are pregnant, and **do not become pregnant during treatment** as this medication may cause major birth defects. Do attend all booked appointments with your dermatologist. Do not hesitate to phone your doctor or dermatologist if you have any concerns about your treatment.

Properties of Roaccutane

- Roaccutane markedly reduces sebum production and shrinks the sebaceous glands.
- It gets rid of comedones and prevents new ones forming.
- Treated skin is dry, inhibiting the growth of acne bacteria.
- It has anti-inflammatory properties.

Indications for treatment

Dermatologists prescribe Roaccutane for patients with acne in the following circumstances:

- Nodular or nodulocystic acne (i.e. where there are large deep lumps)
- Acne conglobata or acne fulminans
- Severe disfiguring inflammatory acne vulgaris
- Acne which is resulting in scarring
- Moderate acne which has failed to respond to topical agents combined with oral antibiotics, or in women, hormonal treatment
- Acne which relapses rapidly on discontinuing treatment
- Acne which has persisted for several years, or arises in an individual over 25 years old
- Dysmorphophobic acne
- When the acne has a significant adverse occupational, social or psychological effect on the patient's life

Dosage

The individual dose prescribed by the dermatologist depends on:

- The patient's body weight
- The specific condition being treated
- The severity of skin condition
- The response to treatment
- Other treatment used at the same time
- The severity of side effects

For severe acne, the total dose over a course of treatment is ideally between 120 and 150-mg/kg-body weight. The range of doses used each day for acne is 0.1 to over 1mg/kg body weight. Generally the side effects are easier to cope with if one starts with a reasonably small dose, perhaps 0.5mg/kg/day. The dose can be gradually increased over the next few weeks depending on tolerance and its effect on the skin condition. Sometimes it needs to be reduced or even temporarily stopped. Your dermatologist will advise you.

The medication requires fat to help its absorption into the bloodstream so it is taken after food. This can be as a single daily dose after the main meal of the day, swallowed with water or another non-alcoholic drink.

If you forget your daily dose, do not double up the next day. The occasional missed dose will not make much difference to the outcome of the treatment.

Drug interactions

Roaccutane should not be taken with the following medications:

- Vitamin-A (retinoic acid) - side effects could be severe. Beta-carotene (provitamin-A) is permitted.
- Tetracyclines (including doxycycline, minocycline, and tetracycline) - these could increase the risk of headaches and blurred vision due to raised intracranial pressure.

Side effects

Unfortunately Roaccutane can make acne worse at first. Usually the flare-up lasts only a couple of weeks, but in some people the flare-up can be very severe and occur for several months. If you have a severe flare-up of your skin condition, let your dermatologist know straight away.

Additional medication such as oral steroids, antibiotics or acne surgery (cautery of comedones) may be required, and the dose of Roaccutane may need to be adjusted.

All treated patients suffer from some side effects. The range and severity of the side effects depends on the disease being treated, the dose of Roaccutane and personal factors. Contact lens wearers have more problem with dry eyes; those with a history of eczema may find Roaccutane aggravates it; fair skinned people burn more easily; sportsmen may have more problems with muscles and joints aching.

If the side effects are troublesome, they will be easier to cope with on a lower dose of Roaccutane. They clear up completely within a few days to a month after the medication has been discontinued. Discuss your side effects with your dermatologist.

The majority of side effects are mucocutaneous i.e. they affect the skin and mucous membranes:

- Dry and cracked lips (cheilitis) affect all treated patients. Apply a lip balm frequently and liberally. Petroleum jelly can be applied indoors or at night. A lip preparation with a sunscreen is preferred during the day. Topical antibiotic such as mupirocin or fusidic acid may be required.
- Dry skin: especially on exposed skin (face, neck, arms, and hands). Apply an emollient cream frequently and liberally to dry skin, especially after bathing.

- Dry nostrils: use petroleum jelly. Do not pick the dry scabs. Nosebleeds may occur in those disposed to them. If this occurs put your head forward and pinch the fleshy part of your nose firmly. Do not swallow the blood (this could make you feel sick). The bleeding usually stops within a few minutes. Topical antibiotic may reduce nosebleeds.
- Dry eyes: severely dry eyes are sore and red. There is a risk of conjunctivitis and/or keratitis, an inflammatory condition of the cornea. Rarely, this scars. Stop your Roaccutane and contact your dermatologist if you have sore red eyes that fail to improve with "artificial tears" (eye drops). Sometimes, paradoxically, patients complain of watery eyes. Do not start wearing contact lenses for the first time while you are taking Roaccutane.
- Dry genitals and anal mucosa: bleeding at the time of a bowel motion may occur from a split anus. Sexual intercourse may be uncomfortable: use plenty of suitable lubrication such as K-Y Jelly or Silk.
- Fragile skin: minor injuries such as grazes occur more readily and heal more slowly. Shave rather than wax: the top layer of your skin may strip off as well the hairs!
- Increased sweating: keep cool.
- Facial erythema (redness) &/or flushing: most noticeable in fair skinned people.
- sunburn: a particular problem for fair skinned people. Careful sun protection is most important. All the year round, make sure you apply a cream-based sunscreen before going outdoors. Apply it frequently and liberally if you are skiing in the spring at high altitude, or if outside during the summer months between 11 am and 5 pm. Do not expose your skin to a sun bed or sun lamp.
- Eczema: red itchy patches may appear on the dry skin. A topical steroid may be required for a few days to clear the rash: obtain a prescription from your doctor or dermatologist. Apply emollients liberally and frequently.
- Impetigo: a secondary infection with *Staphylococcus aureus* and/or *Streptococcus pyogenes* bacteria. Impetigo is also known as "school sores"; there are yellowish crusted patches, most often around the lips and nostrils or affecting the acne spots. See your doctor for a course of topical and/or oral antibiotics.
- Pyogenic granuloma: red juicy lumps may rarely appear around acne nodules or elsewhere. See your dermatologist for treatment (topical steroids & cautery).
- Paronychia: an infection of one or more nail folds, usually with *Staphylococcus aureus*. It is especially common in ingrowing toenails or nails that are chewed or picked. Paronychia can be particularly stubborn and resistant to treatment but settles once the Roaccutane has been discontinued.
- Hair loss: some hair may fall out temporarily, and the hair may lose condition. It grows normally once the Roaccutane has been stopped. Normal shampoo and conditioners may be used but won't influence the hair fall. If the scalp is scaly, an anti-dandruff shampoo twice a week may help.
- Nail changes: the nails may become brittle and slow growing. They recover when treatment has been discontinued, but it will take several months for the new healthy nail to grow out.

Adverse effects of Roaccutane



Acne flare early
in the course of
Roaccutene



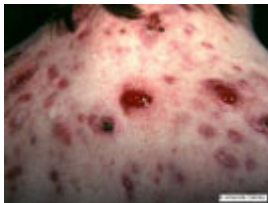
Dry lips on
Roaccutene



Sunburn aggravated
by Roaccutane



Dermatitis due
to Roaccutane



Granulomas provoked by
Roaccutene
in a patient with acne
conglobata



Staphylococcal impetigo
complicating a course
of Roaccutene



Infected nailfold
(paronychia) due
to Roaccutene

Other side effects:

- Headache: generally mild and responding to paracetamol. Severe headache associated with blurred vision could indicate raised intracranial pressure, a rare but severe side effect. Contact your dermatologist or general practitioner if this occurs to you.
- Muscle aches (myalgia) especially after exercise. Low backache is not uncommon. Joint aches (arthralgia) especially after exercise can sometimes be debilitating. These symptoms respond to nonsteroidal anti-inflammatory drugs such as ibuprofen.
- Tiredness (lethargy and drowsiness) is common; it responds to a good night's sleep.
- Mood changes and depression may occur (rarely). If this occurs, seek help immediately from your dermatologist or general practitioner. Severe depression is very rare but may require the Roaccutene to be discontinued. Antidepressant medications may be helpful.
- Eye problems: night blindness and slow adaptation to the dark. This arises because Roaccutene replaces retinoic acid on receptors on the rods, the cells in the retina that enable us to see in poor light. Drivers may experience increased glare from car headlights at night. If you have eye problems, do not drive or pilot a plane after dark. Discuss your visual problems with your dermatologist; a lower dose of Roaccutene may be advised or you may need to consult an ophthalmologist. Cataracts have rarely been reported.
- Hypertriglyceridaemia (high blood fats) can result in pancreatitis, a painful and dangerous condition. Make sure you follow a low-fat diet while you are on Roaccutane and avoid

simple carbohydrates (sugar, sweet drinks, lollies etc). Have blood tests as advised by your dermatologist and make sure you have found out whether the results are normal or not. If your blood fats rise significantly on Roaccutane you may have to reduce the dose or discontinue the treatment.

- Diarrhoea or bleeding from the bowel may rarely occur, especially in those with colitis.
- Irregular or heavier menstrual periods may sometimes occur. This is not harmful. If you miss a period, make sure you are not pregnant by having a blood or urine test.
- Allergy to Roaccutane. This is rare but may include liver disease and a febrile illness. High-tone deafness, vasculitis and urticaria have rarely been reported.

Mood Change

Although Roaccutane has been available since 1982, there is still no clear cut evidence that Roaccutane can cause depression. Changes in mood have been reported in patients taking Vitamin A, etretinate and Roaccutane. Such symptoms have been reported in the treatment of patients with acne, disorders of keratinisation and in patients with cancer given isotretinoin. Vitamin A and its metabolites do cross the blood/brain barrier, can induce benign intracranial hypertension and cause headache, and so there are no theoretical reasons why mood alteration could not occur. However, the data supporting such a link are either anecdotal or based on small inconclusive studies, often with significant design faults. In particular it has not been possible to distinguish accurately between mood change due to the drug and to the acne itself.

The problem is not a new one. Beginning in 1983, there have been a number of case reports, some well publicised, as well as small case studies. These suggest that mood change, and particularly depression, can occur during or soon after the use of Roaccutane. Hard evidence is not available, but the small number of studies in which patients with apparent mood change were rechallenged with Roaccutane and had a relapse of mood alteration is the most compelling. Seven of 700 Roaccutane-treated patients were described to have psychiatric symptoms in a case series by Scheinman et al. The most common symptoms reported have been fatigue, irritability, poor concentration, sadness, crying spells, loss of motivation and forgetfulness. The time course of onset of mood alteration is variable, but is often later in treatment, and in some cases, depressive symptoms have only occurred in second or even third courses of therapy. Resolution of symptoms is usually rapid - within days to weeks of discontinuing the drug -, although there are instances of prolonged illness requiring antidepressive therapy. Not all patients have stopped therapy on developing depressive symptoms: some have elected to continue with Roaccutane and have improved psychologically without additional antidepressive therapy, and others have received psychological support and/or antidepressant medication. The frequency of suicidal behaviour appears to be very small - 37 suicides in 5 million individuals exposed in the USA between 1982 and 2000. This figure may be an under-estimate because of under-reporting since the numbers increased after the FDA warning in 1998, but if true it is lower than the estimated suicide rate for individuals of comparable age and sex distribution. It is important to be aware that suicidal behaviour can occur with psychotic conditions other than depression.

On a similar more positive note, there is a larger study of 7195 patients treated with Roaccutane compared with 13,700 treated with antibiotics drawn from Canadian and UK database examining the risk of depression and suicide in these patients with acne. The UK data are unreliable because they relied upon the recording of Roaccutane therapy by GPs who are not responsible for prescribing it, and there was selection bias in the ascertainment of mental disorders. This study concluded that **neither depression nor suicide were more common in patients treated with Roaccutane**, but

was not sufficiently large to confirm this reliably for suicide, nor for depression if the UK data is excluded. It was not designed to answer the question of whether having acne itself could cause mood disorders or depression, although some studies have indicated this may happen.

From the available data, it is unclear whether those patients with a pre-treatment history of depression may be more at risk. The frequency of pre-treatment anxiety and associated psychological traits both in the individual affected and their family is strikingly high (60 -70%) in those cases reported to the American FDA. There are also reports of apparently spontaneous and idiosyncratic mood alteration in individuals without a preceding history of psychiatric disease. Conversely, there are data indicating an improvement in psychiatric well being in patients with acne as their skin disease has improved after receiving isotretinoin

In summary, there are **unproven suggestions** that Roaccutane can produce mood change: this has been reported in patients with or without preceding psychiatric illness, and thus far there are no predictive tests that allow the level of risk (if any) to be quantified.

In the absence of a definitive study large enough to detect what all agree is at worst a very uncommon effect (requiring around 8000 subjects), for now, we suggest that:

- i). A direct enquiry about previous psychiatric health should be made of all patients who are being considered for Roaccutane and the facts recorded fully in the notes.
- ii). All patients, and their parents in the case of minors and adolescents, should be made aware of the potential for mood change in a realistic, non-judgemental way, and should be advised to ask their family and friends to comment if such change should occur.
- iii). Direct enquiry about psychological symptoms should be made at each clinic visit. Suggested screening questions might be:

For most of the last 2 weeks...

- a) Have you been feeling unusually sad or fed up?
- b) Have you lost interest in things that used to interest you, or gave you pleasure?

- iv). If symptoms of depression or mood change do occur, then ideally, Roaccutane treatment should be discontinued. However, some patients, after discussion, may wish to continue with the drug because of the benefit to their skin. In this case, specialist psychiatric support should be obtained.
- v). If serious psychiatric disease is suspected, there should be an immediate referral to the psychiatric services.

Monitoring

Most patients are advised to have blood tests before and on one or more occasions during Roaccutane treatment. Patients with certain serious health problems may be advised against taking Roaccutane, or may be treated with a lower dose than usual. Such health problems include severe liver or kidney disease, high blood fats, diabetes and depression. The tests may include:

- Pregnancy test (beta-HCG) for women and girls of child-bearing potential (you will probably be asked to have this performed even if you tell your dermatologist you are not sexually active, still a teenager, or your partner has been sterilised). Please do not be offended.
- Blood fats (cholesterol and triglyceride levels). These are most reliable if measured on a fasting sample, i.e. no food for some hours (perhaps first thing in the morning, eating your breakfast after the test has been completed).

- Liver function tests. Occasionally, Roaccutene may disturb liver function; this requires monitoring but if the reaction is mild the drug can usually be continued. Rarely, it causes a symptomatic hepatitis: the drug must then be discontinued. Drink minimal alcohol while taking Roaccutene, as alcohol also affects the liver.
- Blood count: this is to check for anaemia and to monitor white cell count and platelets (clotting cells).

Contraception and pregnancy

Roaccutene **must not** be taken in pregnancy because of a very high risk of serious growth abnormalities in the baby.

It should **not** be taken during breast-feeding as it enters the breast milk and might affect the baby.

You must tell your dermatologist if you think you may be pregnant before you start on Roaccutene. If you intend getting pregnant within the next six months or so, you should not take Roaccutene.

All females who could biologically have a child should take the following precautions during treatment with Roaccutene and for four weeks after the medication has been discontinued:

- Abstinence. The most reliable method of avoiding pregnancy is not to have sex. No method of contraception is completely reliable. "Natural" family planning is particularly risky.
- If sexually active, **two reliable methods of contraception** should be used. Discuss contraception with your doctor (general practitioner, family planning specialist, gynaecologist or dermatologist). The combined oral contraceptive, IUD (intrauterine device) combined with condoms or "the injection" (medroxyprogesterone or Depo-Provera) may be suitable. Roaccutene may reduce the efficacy of these medicines in some women, and they are not 100% reliable. Subcutaneous hormone implants or Mirena® may also be considered.
- A prescription for emergency contraception (a high dose of progesterone, trade name Levonelle) can be obtained from a medical practitioner (GP or family planning clinic) or accredited pharmacy. It prevents 85% of pregnancies if taken within 72 hours of unprotected sexual intercourse.
- If your contraception fails, termination of pregnancy (an abortion) may be advised if pregnancy arises during treatment with Roaccutene or within a month of discontinuing it. Do not put yourself in this situation!
- Roaccutene has a very high chance of resulting in a spontaneous miscarriage or a severe birth deformity if a fetus is exposed to it during the first half of pregnancy. The deformities affect the growth of tissues developing at the time of exposure to the drug:
 - Cranium (skull and brain)
 - Cardiac (heart)
 - Eye, ear
 - Limbs

Males and females: Do not give blood while you are on Roaccutene or for a further four weeks after you have discontinued it, in case your blood is used for a pregnant woman.

Males. Roaccutene has no effect on sperm or male fertility and has not been shown to cause birth defects in children fathered by men taking it. No specific contraceptive precautions are necessary for men.

Children. Children can take Roaccutene if necessary to control severe skin disease.

Slow responders

Some patients with acne respond unexpectedly slowly and incompletely to Roaccutane. The reasons are thought to be:

- Large comedones ("macrocomedones")
- Nodules
- Secondary infection with *Staphylococcus aureus*
- Unknown factors

Options available to slow responders include:

- Cautery or diathermy of comedones
- Prolonged course of Roaccutane
- Additional treatment with oral antibiotics

Treatment of relapses

At least fifty per cent of patients with acne are lucky enough to have a permanent cure after a single course of Roaccutane. Unfortunately, in some patients, acne recurs few months to a few years after the medication has been discontinued.

If indicated, these patients may receive one or more further courses of Roaccutane. This may be at a similar dose and duration as before, or it may differ from previously.

A small number of people with particularly troublesome skin conditions require long term treatment with Roaccutane. With the exception of patients with skin cancers due to immunosuppressive medications eg organ transplant patients (who required 0.5 to 1mg/kg/day), generally only a small dose is required, such as 20 mg twice weekly. Another regime is to take 0.5-1 mg/kg/day for one week out of every four weeks for a minimum of six monthly cycles. These regimes may be used for patients with:

- Persistent acne (all types)
- Severe seborrhoea
- Rosacea
- Scalp folliculitis

Besides the worry about pregnancy in treated women, the main concern with long term treatment is that Roaccutane may have effects on the bones. Diffuse interstitial skeletal hyperostosis ("DISH"), a normal and common ageing process may be accelerated in those taking excessive doses of Roaccutane for long periods. The result can be seen on X-rays of the affected bones and includes spurs on the heel, knee, and spine. DISH may result in aching discomfort, which does not necessarily resolve when Roaccutane is discontinued.