Roaccutane®

Isotretinoin

Composition

Active substances

Isotretinoin (13-cis-retinoic acid).

Excipients

Soft capsule core (10 mg):

Yellow beeswax , hydrogenated soya-bean oil * (7.68 mg), partially hydrogenated soya-bean oil * (30.72 mg), refined soya-bean oil * (107.92 mg).

Soft capsule core (20 mg):

Yellow beeswax , hydrogenated soya-bean oil * (15.36 mg), partially hydrogenated soya-bean oil * (61.44 mg), refined soya-bean oil * (215.84 mg)

*produced from genetically modified soybean

Soft capsule shell:

Gelatin, glycerol, sorbitol E420 (3.05 mg for the 10 mg soft capsules and 4.86 mg for the 20 mg soft capsules), mannitol, hydrogenated hydrolysed starch, titanium dioxide, red iron oxide.

Ink:

Lacquer, black iron oxide, propylene glycol.

Pharmaceutical form and active substance quantity per unit

Soft capsules containing 10 mg of isotretinoin

Soft capsules containing 20 mg of isotretinoin

Indications/Uses

Severe forms of acne (such as nodular acne, acne conglobata or acne with the risk of permanent scarring) that have proved resistant to adequate standard treatment courses with systemic antibiotics and topical therapy.

Dosage/Administration

Roaccutane should only be prescribed by, or under the supervision of, physicians who are familiar with the use of systemic retinoids in the treatment of severe acne and have a thorough knowledge of the risks of isotretinoin therapy and the necessary monitoring measures.

Usual dosage

The therapeutic response to Roaccutane and some of its side effects are dose-dependent and vary between patients. Individual dose adjustments are therefore necessary during treatment.
Roaccutane therapy should be initiated at a dose of 0.5 mg/kg body weight daily. In most patients, the dose is between 0.5 and 1.0 mg/kg body weight daily. In patients with very severe acne or truncal acne, a higher daily dose of up to 2.0 mg/kg body weight may be needed.
A cumulative dose of 120 mg/kg body weight per treatment course was shown to increase remission rates and prevent recurrence, with no additional substantial benefit to be expected above this level (120-150 mg/kg body weight).

Duration of treatment

Treatment duration in a patient therefore varies with the daily dose employed. Complete remission of acne is normally achieved with a treatment duration of 16-24 weeks. In most patients, complete resolution of acne was achieved with a single treatment cycle. In the event of definite relapse, a repeat course of Roaccutane can be administered at the same daily and cumulative treatment dose as before. Since further improvement in the acne can still be observed for up to 8 weeks after completing treatment, repeat treatment should not be initiated until this period has elapsed.

Special dosage instructions

Patients of reproductive potential

Pregnancy tests

Women of childbearing potential must take pregnancy tests before starting treatment with Roaccutane, during treatment and 5 weeks after the end of treatment (see "Warnings and precautions – Pregnancy Prevention Programme").

Contraception

Since Roaccutane is teratogenic, women of childbearing potential must follow the Pregnancy Prevention Programme (see "Warnings and precautions – Pregnancy Prevention Programme").

Women of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent method) or two preferably complementary user-dependent methods of contraception (including a barrier method). Contraception must be used for at least one month before the start of treatment and throughout the treatment period, and should be continued for at least one month after completing treatment with Roaccutane, including in patients with amenorrhoea (see "Warnings and precautions – Pregnancy Prevention Programme").

Patients with intolerance

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequence of a longer treatment duration and a higher risk of relapse. To achieve the best possible effect in these patients, treatment should be continued at the highest tolerated dosage.

Concurrent topical treatment

Concurrent use of other keratolytic or exfoliative anti-acne drugs or UV phototherapy is not indicated.

Patients with renal impairment

Experience in patients with severe renal failure is very limited (see "Warnings and precautions"). If treatment with Roaccutane is nevertheless given, it should be started at a dose of 10 mg daily and then individually adjusted on the basis of tolerability.

Children and adolescents

Roaccutane is not indicated for the treatment of prepubertal acne. Use in children under 12 years of age is not recommended.

Mode of administration

The soft capsules should be taken once or twice daily with meals.

Contraindications

Roaccutane is contraindicated in pregnant and breast-feeding women (see "Warnings and precautions" and "Pregnancy, lactation").

Roaccutane is contraindicated in women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met (see "Warnings and precautions" and "Pregnancy, lactation").

Roaccutane is also contraindicated in patients with hypersensitivity to isotretinoin or any of the excipients. Roaccutane contains soybean oil, partially hydrogenated soybean oil and hydrogenated soybean oil.

It must not be taken/used if patients are hypersensitive (allergic) to peanut or soya.

Roaccutane is also contraindicated in patients

- who are hypersensitive to the active substance or any of the excipients,
- with hepatic impairment,
- with pre-existing hypervitaminosis A,
- with markedly elevated blood lipid levels, and

- who are receiving concomitant treatment with tetracyclines.

Warnings and precautions

Roaccutane is highly **TERATOGENIC**. There is an extremely high risk of serious and life-threatening malformations in the child if pregnancy occurs while taking Roaccutane at any dosage and for any length of time. Potentially all exposed fetuses may be affected.

Roaccutane is contraindicated in women of childbearing potential unless the patient meets all the conditions of the Pregnancy Prevention Programme.

Patients must be informed both orally and in writing about the need for strict contraception.

Pregnancy Prevention Programme

The patient must meet the following conditions:

- She has a severe form of acne (see "Indications/Uses").
- The physician has evaluated the possibility of pregnancy with the patient.
- The patient understands the teratogenic risk.
- She is informed about and understands the dangers to the unborn child if she becomes pregnant during or within one month of completing treatment with Roaccutane. She is willing to be examined without delay if there is a risk that she has become pregnant.
- She understands and accepts the need for effective contraception without interruption for one month before starting treatment with Roaccutane, during treatment and for one month after completing treatment. At least one highly effective method of contraception (i.e. a user-independent method) or two preferably complementary user-dependent methods of contraception (including a barrier method) must be used. She must be warned about the possibility of contraceptive failure.

- In each case, personal circumstances should be considered and the patient herself should be involved in choosing the method of contraception to ensure compliance with the chosen measures and adherence to treatment.
- Even if she has amenorrhoea, the patient must follow all instructions for effective contraception.
- The patient is able to carry out the contraceptive measures consistently and reliably.
- A medically supervised pregnancy test must be performed no more than 11 days before the start of treatment and give a negative result.
- She understands the need for, and must agree to take, pregnancy tests before and during treatment and 5 weeks after the end of treatment.
- She must not start treatment with Roaccutane until the second or third day of the next normal menstrual period.
- She understands and accepts the need for rigorous monthly follow-up.
- In the event of relapse treatment, she must also use the same uninterrupted and effective contraceptive measures for 1 month before, during and for 1 month after Roaccutane therapy, and the same reliable pregnancy tests should be performed.
- She must fully understand the precautions and confirm her willingness to comply with the reliable contraceptive measures explained to her.

  These conditions also apply to women who are not currently sexually active unless the prescriber believes there are compelling reasons why there is no risk of pregnancy. Even women who do not normally use contraception because of a history of infertility (except in the case of hysterectomy) or who claim not to be sexually active must be advised to use effective contraceptive measures in keeping with the above guidelines while taking Roaccutane.

The prescribing physician must ensure the following:

- The potential for pregnancy has been individually assessed for each patient.
- The patient must have a severe form of acne (nodular or conglobate acne or acne at risk of permanent scarring) that has not responded to standard treatments with systemic antibacterials and topical therapy.
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.
- The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent method) or two preferably complementary user-dependent methods of contraception (including a barrier method) for at least one month before the start of treatment, followed by effective contraception throughout the treatment period and for at least one month after the end of treatment.
- The patient complies with the conditions for pregnancy prevention listed above and confirms that she adequately understands the instructions.
- The patient has accepted the above conditions.

  Should pregnancy occur despite these precautions during treatment with Roaccutane or in the following month, there is a high risk of very serious fetal malformations (involving in particular the central nervous system, heart and large blood vessels). There is also an increased risk of spontaneous abortion. If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy.

- **Contraception**

  - Female patients must be given comprehensive information on pregnancy prevention and should be referred to a contraceptive advice centre if they are not using effective contraception.

- As a minimum requirement, women of childbearing potential must use at least one highly effective method of contraception (i.e. a user-independent method) or two preferably complementary user-dependent methods of contraception (including a barrier method). Contraception must be continued for at least one month after stopping treatment with Roaccutane, even in patients with amenorrhoea.

- A prescription for Roaccutane should be issued for no more than 30 days of treatment.

- **Pregnancy tests**

In line with standard practice, it is recommended that a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml be performed in the first 3 days of each menstrual period as follows:

- *Before starting treatment:*
  - To exclude the possibility of pregnancy before the start of contraception, it is recommended that a first medically supervised pregnancy test be performed and the date and result documented. In patients without regular periods, this pregnancy test should be timed to reflect the patient's sexual activity and performed approximately 3 weeks after the last unprotected intercourse. The prescriber should explain contraception to the patient.
  - A pregnancy test under medical supervision should also be performed during the consultation at which Roaccutane is prescribed or in the 3 days before the visit to the prescriber, and should be delayed until the patient has been using effective contraception for at least 1 month. The purpose of this test is to make sure that the patient is not pregnant when she begins treatment with Roaccutane.
- *During treatment:*

- Further consultations should be arranged at 28-day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to standard practice, including consideration of the patient's sexual activity and recent menstrual history (abnormal or missed periods or amenorrhoea). Where indicated, follow-up pregnancy tests should be performed on the day Roaccutane is prescribed or in the 3 days before the visit to the prescriber.

- *After treatment:*
  - Five weeks after the end of treatment, the patient should undergo a final pregnancy test to exclude pregnancy.

Pharmacists must keep to the following guidelines:

- Prescriptions of Roaccutane to women of childbearing potential should be limited to no more than 30 days of treatment, and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of Roaccutane should occur on the same day.
- Roaccutane should be dispensed on the day it is prescribed and no later than 7 days after the prescription date.

Educational material

To assist prescribers, pharmacists and patients in avoiding fetal exposure to Roaccutane, the manufacturer will provide educational material reinforcing the warnings about the teratogenicity of isotretinoin, containing advice on contraception before the start of treatment and providing information on the need for pregnancy testing.

For physicians:

- Checklist for physicians/acknowledgement of receipt for prescribing to female patients

For female patients:

- Patient reminder card
- Patient brochure with consent form for female patients

For pharmacists:

- Checklist for pharmacists – guidance for dispensing Roaccutane

Physicians must fully inform all patients, both male and female, about the teratogenic risk and strict contraceptive measures as described in the Pregnancy Prevention Programme.

Further warnings and precautions

All patients, both male and female, should be instructed never to give Roaccutane to another person.

Patients must not donate blood during and for one month after treatment with Roaccutane because there is a potential risk to the fetus in pregnant women who receive such a blood transfusion.

Male patients

The available data suggest that the level of maternal exposure from the semen of male patients receiving isotretinoin is not of sufficient magnitude to be associated with a teratogenic effect by isotretinoin.

Psychiatric disorders

Depression, aggravation of existing depression, anxiety, aggressive tendencies, mood swings, psychotic symptoms and, very rarely, suicide attempts and suicide have been reported in patients treated with isotretinoin (see “Undesirable effects”). Particular care is necessary in patients with a history of depression, and all patients must be monitored for signs of depression and referred for appropriate treatment if necessary. Discontinuation of Roaccutane therapy may be insufficient to relieve the symptoms, and further psychiatric or psychological evaluation may therefore be necessary.

Skin and subcutaneous tissue disorders

An acute exacerbation of acne is occasionally seen at the start of treatment. However, this usually resolves within 7-10 days during continued treatment and does not normally require dose adjustment.

Intensive exposure to strong sunlight or ultraviolet radiation must be avoided. If necessary, a sunscreen with a high sun protection factor (at least SPF 15) must be used.

Aggressive chemical dermabrasion and cutaneous laser treatment must be avoided in patients during treatment with Roaccutane and for at least 5-6 months after the end of treatment because of the risk of hypertrophic scarring in atypical areas and, more rarely, of postinflammatory hyper- or hypopigmentation of the treated areas. Wax epilation must be avoided for a period of at least 6 months after treatment in patients treated with Roaccutane because of the risk of epidermal stripping.

Concomitant use of Roaccutane together with topical keratolytic or exfoliative anti-acne drugs must be avoided, as this could increase local irritation (see “Interactions”).

Patients should be told to use a moisturising skin ointment or cream and a lip balm from the start of treatment onwards, as isotretinoin is likely to lead to dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme [EM], Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) associated with Roaccutane use. These events may be serious and life-threatening, potentially resulting in hospitalisation, disability or death. TEN, if it occurs, usually begins within 4 weeks of starting treatment, generally with symptoms of viral illness such as fever, cough and sore throat. Tender erythematous lesions may develop, which progress to bullae in a matter of hours. If TEN is suspected, Roaccutane therapy should be discontinued.

Eye disorders

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. There have been reports of cases of dry eyes that have not resolved after discontinuation of treatment. The use of a moisturising eye ointment or artificial tears may be useful in the case of dry eyes. Patients may develop an intolerance to contact lenses that makes it necessary to wear glasses during treatment.

Decreased night vision has also been reported (see "Effects on ability to drive and use machines") and was of sudden onset in some patients. Patients with eye problems should be referred to an ophthalmologist for investigation. Discontinuation of treatment with Roaccutane may be necessary.

Hearing impairment

Impaired hearing has been reported in patients treated with Roaccutane. In some cases, this hearing impairment was not reversible on stopping treatment. Treatment with Roaccutane must be immediately discontinued if hearing impairment or tinnitus occurs during treatment with isotretinoin.

Musculoskeletal and connective tissue disorders

Myalgia, arthralgia and elevated serum levels of creatine phosphokinase have been reported in patients receiving isotretinoin, particularly those undertaking strenuous physical activity (see "Undesirable effects").

Bone changes such as premature epiphyseal closure, hyperostosis and calcification of tendons and ligaments have occurred after several years of use at very high doses for treating keratinisation disorders. The dosage level, treatment duration and total cumulative dose in these patients generally far exceeded those recommended for acne therapy.

Sacroiliitis has been reported in patients treated with isotretinoin. In order to distinguish sacroiliitis from other causes of back pain, further examinations, including imaging procedures such as MRI, may be necessary in patients with clinical signs of sacroiliitis. In post-marketing cases, sacroiliitis improved following discontinuation of Roaccutane and appropriate treatment.

Benign intracranial hypertension

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see "Contraindications" and "Interactions"). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual

disturbances and papilloedema. Patients developing benign intracranial hypertension must immediately stop treatment with Roaccutane.

Hepatobiliary disorders

Liver enzymes must be checked before treatment, one month after the start of treatment, and then at 3-monthly intervals, unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases, these changes have been within the normal range and values have returned to baseline levels during treatment. However, if a clinically relevant increase in transaminase levels persists, dose reduction or discontinuation of treatment must be considered.

Renal impairment

Renal impairment and renal failure do not adversely affect the pharmacokinetics of isotretinoin. Roaccutane can therefore be given to patients with renal impairment. It is, however, advisable for such patients to start with a lower dose and gradually increase it to the maximum tolerated dose (see “Dosage/Administration”).

Lipid metabolism

Serum lipids (fasting values) must be checked before treatment, one month after the start of treatment, and then at 3-monthly intervals, unless more frequent monitoring is clinically indicated. Elevated serum lipid levels generally return to normal after dose reduction or treatment withdrawal, and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. If hypertriglyceridaemia cannot be adequately controlled or if symptoms of pancreatitis occur (see “Undesirable effects”), treatment with Roaccutane must be stopped. Levels exceeding 800 mg/dl or 9 mmol/l are sometimes associated with acute pancreatitis, which may be fatal.

The risks and benefits of Roaccutane therapy must be weighed particularly carefully in high-risk patients. This applies to patients with diabetes, overweight, increased alcohol consumption, impaired lipid metabolism or familial dyslipidaemias. More frequent monitoring of lipids and/or

blood glucose is recommended in these patients. The cardiovascular consequences of Roaccutane-induced hypertriglyceridaemia are unknown.

Gastrointestinal disorders

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (bloody) diarrhoea should discontinue Roaccutane immediately.

Allergic reactions

Anaphylactic reactions have been reported in rare cases, sometimes after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Severe cases of allergic vasculitis have been reported, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement. Severe allergic reactions necessitate immediate discontinuation of therapy and careful monitoring.

Fructose intolerance

Roaccutane contains 3.05 mg sorbitol per 10 mg soft capsule and 4.86 mg sorbitol per 20 mg soft capsule.

The additive effect of the concomitant use of medicinal products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) must be considered.

High-risk patients

Patients with diabetes, overweight, alcoholism or lipid metabolism disorder undergoing treatment with Roaccutane may require more frequent checks of serum lipids and/or blood glucose levels. Elevated fasting blood glucose levels have been reported and new cases of diabetes diagnosed during treatment with isotretinoin.

Interactions

Roaccutane should not be administered concomitantly with vitamin A, as this could exacerbate symptoms of hypervitaminosis A.

Since tetracyclines may likewise cause intracranial hypertension (pseudotumor cerebri), their combination with Roaccutane is contraindicated (see "Contraindications" and "Warnings and precautions").
Concomitant use of Roaccutane together with topical keratolytic or exfoliative anti-acne drugs must be avoided, as this could increase local irritation (see "Warnings and precautions").
Oral contraceptives: see "Pregnancy, lactation".

Pregnancy, lactation

Pregnancy

Pregnancy is an <u>absolute</u> contraindication to treatment with Roaccutane (see "Contraindications" and "Warnings and precautions"). Women of childbearing potential must follow the Pregnancy Prevention Programme. Should pregnancy occur despite all precautions during treatment with Roaccutane or within one month after the end of treatment, there is a high risk to the fetus of extremely serious and severe malformations.

Risk to the developing embryo/fetus
Among the fetal malformations associated with isotretinoin exposure are abnormalities of the central nervous system (hydrocephalus, cerebellar malformation, microcephalus), facial dysmorphia, cleft palate, external ear abnormalities (absence of the pinna, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as Fallot's tetralogy, transposition of the great vessels, septal defects), and thymus and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.
If pregnancy occurs in a woman treated with Roaccutane, treatment must be stopped and the patient referred for investigation and counselling to a teratologist or a physician with experience in teratology (see "Warnings and precautions – Pregnancy Prevention Programme").

Lactation

As isotretinoin is highly lipophilic, excretion in human milk is extremely probable. The use of Roaccutane is contraindicated in nursing mothers.

Oral contraceptives

The effect of low-dose progestins may be reduced by interaction with isotretinoin.
For this reason progestin-only preparations (oestrogen-free contraceptives) should not be used.

Effects on ability to drive and use machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted even after treatment (see "Undesirable effects"). As onset was sudden in some instances, patients must be alerted to this potential problem and warned to be cautious when driving or operating machines.
Light-headedness, dizziness and visual disturbances have been reported in very rare cases. Patients should be warned that if they experience these side effects, they should not drive, operate machinery or perform any other activity in which these symptoms could endanger them or other people.

Undesirable effects

Some of the side effects associated with isotretinoin therapy are dose-dependent. The side effects are normally reversible after a dosage change or discontinuation of treatment, but some may persist after the end of treatment. The following symptoms are the most commonly reported undesirable effects of isotretinoin: dryness of the skin, dryness of the mucosae, e.g. of the lips (cheilitis), the nasal mucosa (epistaxis) and the eyes (conjunctivitis).
The frequency categories are listed using MedDRA terminology: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Very rare: Gram-positive bacterial infection (mucocutaneous).

Blood and lymphatic system disorders

Very common: Anaemia, erythrocyte sedimentation rate increased, thrombocytopenia, thrombocytosis.

Common: Neutropenia.
Very rare: Lymphadenopathy.

Immune system disorders

Rare: Allergic skin reactions, anaphylactic reactions, hypersensitivity.

Metabolism and nutrition disorders

Very rare: Diabetes mellitus, hyperuricaemia.

Psychiatric disorders

Rare: Depression, depression aggravated, mood alterations, aggressive tendencies, anxiety.
Very rare: Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide.

Nervous system disorders

Common: Headache.
Very rare: Benign intracranial hypertension, convulsions, drowsiness, dizziness.

Eye disorders

Very common: Blepharitis, conjunctivitis, dry eye, eye irritation.
Very rare: Blurred vision, cataract, colour blindness (decreased colour vision), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia, visual disturbances.

Ear and labyrinth disorders

Very rare: Hearing impairment, tinnitus (see “Warnings and precautions”).

Vascular disorders

Very rare: Vasculitis (e.g. Wegener’s granulomatosis, allergic vasculitis).

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis, nasal dryness, nasopharyngitis.
Very rare: Bronchospasm (particularly in patients with asthma), hoarseness.

Gastrointestinal disorders

Very rare: Colitis, ileitis, dry throat, gastrointestinal bleeding, bloody diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see "Warnings and precautions").

Hepatobiliary disorders

Very common: Transaminases increased (see "Warnings and precautions").
Very rare: Hepatitis.

Skin and subcutaneous tissue disorders

Very common: Cheilitis, dermatitis, dry skin, localised exfoliation, pruritus, erythematous rash, skin fragility (risk of abrasions).

Rare: Alopecia.
Very rare: Acne fulminans, exacerbation of acne (acne flare), erythema (facial), exanthema, hair changes, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased.

Musculoskeletal and connective tissue disorders

Very common: Arthralgia, myalgia, back pain (particularly in adolescent patients).
Very rare: Arthritis, calcification of ligaments and tendons, premature epiphyseal closure, exostosis (hyperostosis), reduced bone density, tendinitis.
Frequency not known: Sacroiliitis.

Renal and urinary disorders

Very rare: Glomerulonephritis.
Frequency not known: Urethritis.

Reproductive system and breast disorders

Not known: Sexual dysfunction including erectile dysfunction and libido decreased, gynaecomastia, vulvovaginal dryness.

General disorders and administration site conditions

Very rare: Granulation tissue (increased formation), malaise.

Investigations

Very common: Blood triglycerides increased, high-density lipoprotein (HDL) decreased.

Common: Blood cholesterol increased, blood glucose increased, haematuria, proteinuria.
Very rare: Blood creatine phosphokinase increased.

The incidence of adverse events was calculated from the total clinical data on 824 patients and from the post-marketing data.

Undesirable effects from the post-marketing phase

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported during the post-marketing period in association with Roaccutane use (see "Warnings and precautions").
Serious cases of rhabdomyolysis, often leading to hospitalisation and some with fatal outcome, have been reported, particularly in patients undertaking vigorous physical activity.
Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction

Overdose

Signs and symptoms

Isotretinoin is a derivative of vitamin A. Even though the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in the event of accidental overdosage.

Symptoms of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar.

Treatment

It may be assumed that such symptoms are reversible and subside without need for treatment.

Properties/Effects

ATC code

D10BA01

Mechanism of action

Isotretinoin, the active substance of Roaccutane, is a synthetic stereoisomer of all-trans-retinoic acid (tretinoin).
The mechanism of action of Roaccutane has not yet been fully elucidated. However, it is clear that the clinical improvement seen in severe acne is associated with a dose-dependent reduction in the activity of the sebaceous glands and a histologically confirmed decrease in their size. Isotretinoin has also been shown to have an anti-inflammatory effect in the skin.
In acne, hypercornification of the epithelial lining of the sebaceous follicle leads to shedding of corneocytes into the duct, resulting in outflow obstruction by keratin and increased accumulation of sebum. A comedo forms and, ultimately, an inflammatory lesion. Roaccutane inhibits the proliferation of sebaceous cells and appears to exert its effect in acne by suppressing normal differentiation. Since sebum is an important substrate for the growth of Propionibacterium acnes, reduced sebum production prevents bacterial colonisation of the sebaceous duct.

Pharmacodynamics

Not applicable.

Clinical efficacy

Not applicable.

Pharmacokinetics

As isotretinoin and its metabolites display linear kinetics, plasma concentrations during treatment can be deduced from values measured after single dosing. This property also indicates that drug-metabolising enzymes in the liver are not induced by isotretinoin.

Absorption

Isotretinoin shows variable absorption from the gastrointestinal tract. Its absolute bioavailability has not been determined because no intravenous dosage form is available for human use. However, extrapolation of results from studies in dogs suggests fairly low and variable systemic bioavailability. In acne patients treated with 80
mg of isotretinoin daily, a steady-state peak blood concentration (C_{max}) of 310 ng/ml (range: 188-473 ng/ml) was observed 2-4 hours postdose under fasting conditions.
If isotretinoin is taken together with food, bioavailability is twice that in the fasting state.

Distribution

Isotretinoin is highly protein-bound, mainly to albumin (≥99.9%). The unbound (i.e. pharmacologically active) fraction of isotretinoin is therefore below 0.1% over a wide therapeutic concentration range.
Isotretinoin plasma levels are approximately 1.7 times blood levels due to poor penetration of isotretinoin into red blood cells.
The volume of distribution of isotretinoin in man has not been determined because no intravenous dosage form is available for human use.
At steady state the isotretinoin blood concentrations ($C_{min,ss}$) in patients with severe acne treated with 40 mg twice daily were 120-200 ng/ml.
In these patients, the concentration of 4-oxo-isotretinoin, a very important metabolite, was more than twice that of isotretinoin.
Little is known about the distribution of isotretinoin in human tissue. The isotretinoin concentration in the epidermis is only half the serum concentration.

Metabolism

After oral administration of isotretinoin, five major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans-retinoic acid), 9-cis-retinoic acid, 4-oxo-tretinoin and 4-oxo-9-cis-retinoic acid.

Of these, 4-oxo-isotretinoin has the highest plasma concentration at steady state, which is higher than the plasma concentration of the parent compound. Further metabolites – including glucuronide conjugates – have been detected but not all completely identified.

Isotretinoin metabolites have shown biological activity in various in vitro tests. The clinical profile observed in patients could therefore reflect the pharmacological effect of both isotretinoin and its metabolites.

A clinical study in 74 patients demonstrated that orally administered 4-oxo-isotretinoin significantly reduces baseline sebum excretion, thus confirming that 4-oxo-isotretinoin is a significant contributor to the activity of Roaccutane. In this study, oral administration of 4-oxo-isotretinoin did not affect endogenous concentrations of isotretinoin and tretinoin, suggesting that the activity of 4-oxo-isotretinoin is mediated by 4-oxo-tretinoin.

Since isotretinoin and tretinoin (all-trans-retinoic acid) are reversibly converted to one another, the metabolism of tretinoin is closely linked with that of isotretinoin. Evidence of presystemic metabolism of isotretinoin has been shown in a clinical study in 10 volunteers. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerisation. It may be assumed from studies in dogs that presystemic metabolism also plays a considerable role in humans.

In vitro metabolic studies have demonstrated that several cytochrome P-450 enzymes are involved in the conversion of isotretinoin to 4-oxo-isotretinoin and of tretinoin to 4-oxo-tretinoin. No single isoform appears to have a predominant role in this regard. Given the varied involvement of cytochrome P-450 enzymes, interactions with isotretinoin and its metabolites would not be expected.

Elimination

Roughly equal proportions of the dose were recovered in urine and faeces after oral administration of radiolabelled isotretinoin. The mean terminal elimination half-life of the unchanged drug after oral administration of isotretinoin in acne patients is 19 hours.
The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean of 29 hours.
Isotretinoin is a naturally occurring retinoid. Endogenous retinoid concentrations are reached within about two weeks after stopping Roaccutane therapy.

Kinetics in specific patient groups

Hepatic impairment

Since isotretinoin is contraindicated in patients with hepatic impairment, little information is available on isotretinoin kinetics in these patients.

Renal impairment

Renal failure does not lead to a relevant reduction in the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

Preclinical data

Genotoxicity

Isotretinoin has not been found to be mutagenic in either in vitro experiments or in vivo animal studies.

Carcinogenicity

Studies of isotretinoin in the rat revealed no carcinogenic properties of isotretinoin.

Reproductive toxicity

Like other vitamin A derivatives, isotretinoin is teratogenic and embryotoxic in animal studies (see “Contraindications”, “Warnings and precautions” and “Special dosage instructions”).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") listed on the pack..

Special precautions for storage

Do not store above 30 °C.

Keep the container in the outer carton to protect the contents from light and moisture.

Keep out of the reach of children.

Instructions for handling

Any Roaccutane soft capsules unused after the end of treatment or by the expiry date must be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal

Packs

Roaccutane 10 mg soft capsules: 30 soft capsules [A]
Roaccutane 20 mg soft capsules: 30 soft capsules [A]
Not all concentrations are marketed in all countries.

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at November 2022

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Catalent Germany Eberbach GmbH, Eberbach, Germany